19th Annual Meeting, American College of Chest Physicians
New York City, May 28 - 31, 1953

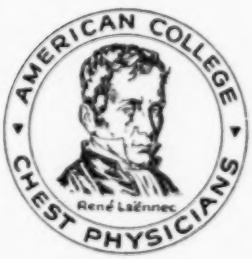
VOLUME XXIII NUMBER 2

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



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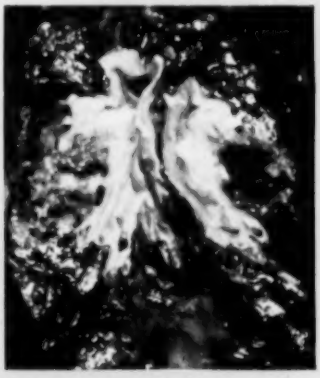

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VOLUME XXIII FEBRUARY 1953 NUMBER 2

CONTENTS:

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1. Kaufman, R., and Farmer, L. (1951), Norisodrine by Aerohalor in Asthma, Ann. Allergy, 9:89, January-February.
2. Swartz, H. (1950), Norisodrine Sulphate (25 Per Cent) Dust Inhalation in Severe Asthma, Ann. Allergy, 8:488, July-August.
3. Krasno, L., Grossman, M., and Ivy, A. (1949), The Inhalation of 1-(3',4'-Dihydroxyphenyl)-2-isopropylaminoethanol (Norisodrine Sulfate Dust), J. Allergy, 20:111, March.

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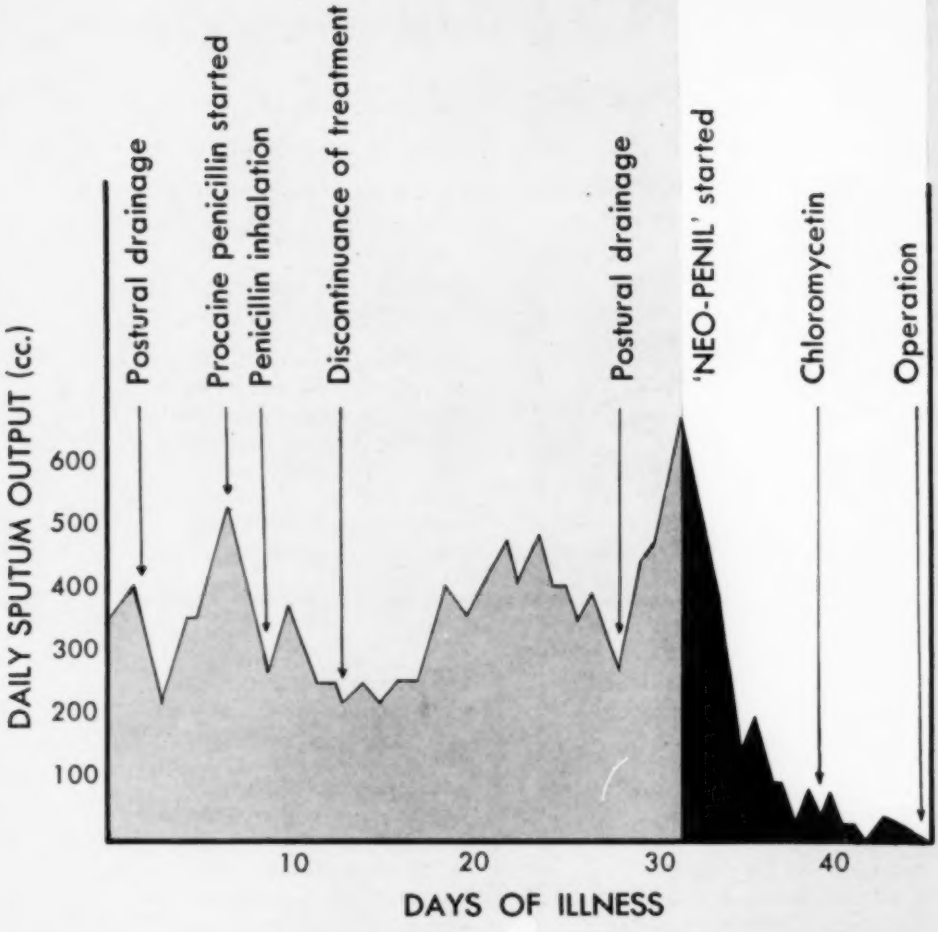
Response: The amount of expectorate decreased but slightly.

On December 4, the patient was transferred to the Department of Thoracic Surgery of a larger hospital, for operation. Bronchoscopic examination revealed marked bronchiectasis in all segments of the left lower lobe. The upper lobe, including the lingula, showed no abnormality. The sputum volume was now 600 cc. per day.

Second course of treatment: In the hope of reducing the sputum volume before operation, the patient was given 'Neo-Penil', intramuscularly, 1 million units the first day, 1 million units b.i.d. the second day, and 1 million units t.i.d. thereafter. Postural drainage was reinstituted.

Response: After 6 days, sputum volume was reduced from 600 cc. to 50 cc. per day. At this time sputum culture revealed penicillin-resistant bacteria and Chloromycetin was given, 0.5 Gm. every 6 hours for 5 days. The sputum volume was further reduced, and it was felt safe to operate.



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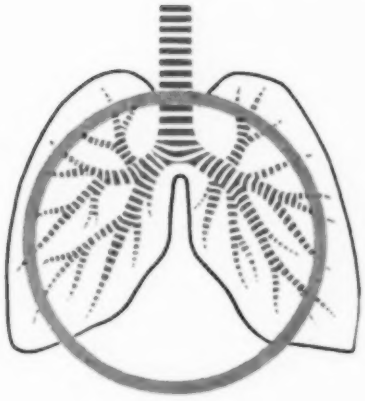

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(1) Bordley, J. E., et al.: Bull. Johns Hopkins Hosp. 85: 396, 1949; (2) Rose, B., et al.: Canad. M. A. J. 62: 6, 1950; (3) Randolph, T. G., and Rollins, J. P.: In Proceedings of First Clinical ACTH Conference, edited by J. R. Mote. Philadelphia, The Blakiston Co., 1950, p. 479; (4) McCombs, R. P., et al.: Bull. New England M. Center 12: 187, 1950; (5) Baldwin, H. S., and DeGara, P. F.: J. Allergy 23: 15, 1952; (6) McCombs, R. P.: New England J. Med. 247: 1, 1952.

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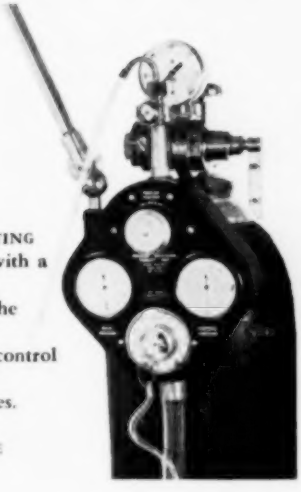

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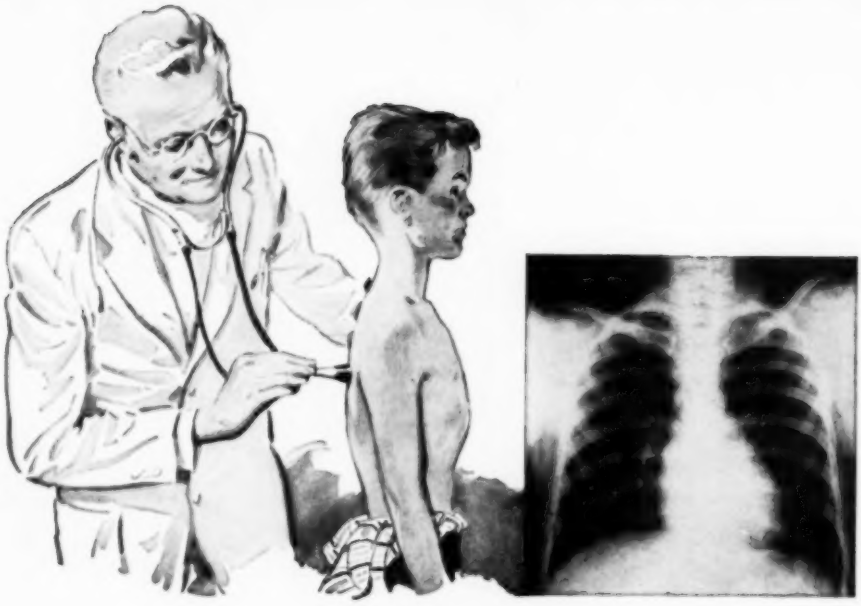

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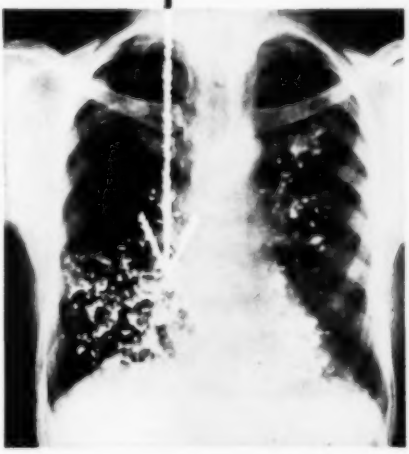

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1. Yater, W. M. Fundamentals of Internal Medicine, ed. 3, New York, Appleton-Century-Crofts, 1949, p. 315.
2. Myers, J. A., and McKinlay, C. A.: The Chest and the Heart, Springfield, Ill., Charles C Thomas, 1948, p. 307.
3. White, B. V., and Geschickter, C. F.: Diagnosis in Daily Practice, Philadelphia, J. B. Lippincott Co., 1947, p. 419.

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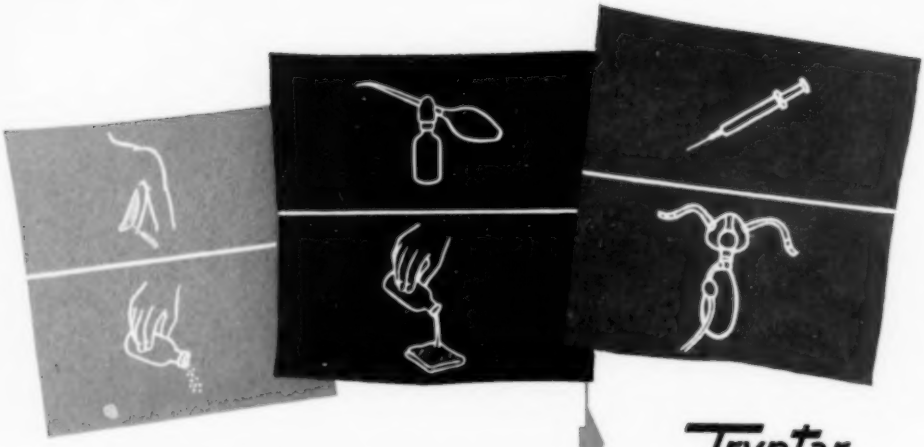

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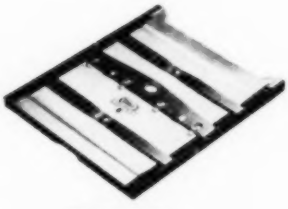

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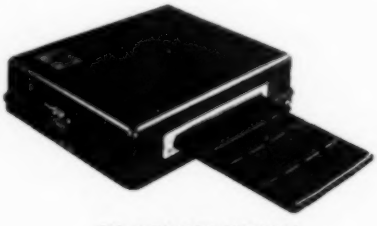

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DISEASES *of the* CHEST

VOLUME XXIII FEBRUARY 1953 NUMBER 2

The Therapeutic Use of Diethylaminoethyl Ester Hydroiodide of Penicillin G in Chronic Bronchopulmonary Infections. Clinical and Bacteriological Studies*

ALVAN L. BARACH, M.D., F.C.C.P., HYLAN A. BICKERMAN, M.D., HARRY M. ROSE, M.D. and GEORGE W. MELCHER, JR., M.D.
New York, New York

Introduction

The treatment of chronic infection of the respiratory tract presents a challenging problem. Except in cases suitable for extirpation of diseased lung tissue, the medical management of chronic bronchitis and bronchiectasis in the pre-antibiotic era attempted for the most part to facilitate drainage of the tracheobronchial tree. Although aerosol therapy with the sulfonamides was accompanied by significant improvement in bronchopulmonary suppuration, including lung abscess,[1,2] the use of these drugs orally generally proved disappointing except in acute exacerbations of infection caused by a gram positive, sulfonamide sensitive organism. Penicillin by parenteral administration was found to be more effective, but arrest of chronic infection was not achieved in the brief periods in which it was given by intramuscular injection. The use of the broad-spectrum antibiotics was generally followed by prompt and conspicuous improvement, manifested by reduction in sputum and cough and by temporary eradication of infection; the occasional development of new infections with organisms relatively insensitive to antibiotics currently available, observed especially in debilitated patients, indicated the need for careful regulation of prolonged therapy with aureomycin, terramycin and chloromycetin.[3,4]

The association of bronchial asthma and pulmonary emphysema with chronic lung infection frequently results in serious impairment of ventilatory function due to inflammation of the bronchial mucosa, with hyperemia and edema of the bronchial walls and peribronchial tissue, increased bronchiolar constriction as well as the tendency towards stag-

*From the Department of Medicine, College of Physicians and Surgeons, Columbia University, the Presbyterian Hospital and the Columbia Division, Goldwater Memorial Hospital, New York.

Drug was supplied by Smith, Kline and French Laboratories, Philadelphia, with the trade name Neo-Penil.

nation of purulent material and localized atelectasis. Since gram positive bacteria were responsible for the majority of cases of infection, penicillin has been widely used in these cases.

The clinical effectiveness of penicillin in the treatment of chronic bronchitis and bronchiectasis was found to be enhanced by its administration as an aerosol, since topical deposition on the diseased bronchial mucosa, in addition to the systemic absorption of the drug via the pulmonary capillary bed, was obtained. In recent studies, including a review of the literature, the value of nebulized penicillin seemed dependent on the maintenance of a high penicillin level locally in the bronchial secretions; this was especially manifest in bronchopulmonary infections due to resistant Staphylococcus aureus.[3,4] In the clinical application of penicillin aerosol, it was noted that bronchospasm at times interfered with completion of therapy in patients with chronic bronchitis associated with either bronchial asthma or pulmonary emphysema. A considerable portion, approximately 20 per cent, developed increasing wheezing following inhalations of penicillin.[4] Because of this complication, it is now customary in our clinic to treat these patients with parenteral penicillin and reserve the use of aerosol penicillin for patients with bronchiectasis, lung abscess, sinusitis and bronchitis or pneumonitis due to resistant Staphylococcus aureus.

The isolation and use of the diethylaminoethyl ester of penicillin by Jensen et al.[5-7] and the demonstration of appreciable levels of penicillin in the bronchial secretions following the intramuscular injection of this drug prompted this study on its clinical effectiveness in chronic bronchopulmonary infection.

The first esters of penicillin were prepared in an impure state by Meyer, Hobby and Chaffee.[8,9] The methyl, ethyl, n-butyl and benzhydryl esters, when tested in vitro against a hemolytic streptococcus, were found to have less than one-tenth of the activity of the material from which they were prepared. Subsequently, these esters were found to be highly effective in mice which were capable of hydrolyzing the esters with the slow liberation of active penicillin.[10] Since other animals and man were incapable of hydrolyzing these esters, it was concluded that they possessed no therapeutic value. In 1948 Carpenter[11] prepared the dimethylaminoethyl ester of penicillin which was followed by the synthesis of the diethylaminoethyl ester as the hydrochloride and hydriodide salts of benzyl penicillin by Jensen, Dragsted and Diaer.[5] In their animal and human studies, the intramuscular injection of the ester resulted in a lower level of penicillin in the serum than a comparable dose of sodium or procaine penicillin, but its concentration in lung tissue was five to eight times higher. Furthermore, penicillin was found in the expectoration in effective concentrations ranging between 0.23 to 0.45 units per cc. whereas little or no penicillin was recovered from the sputum after the injection of procaine penicillin.

In an extension of this work, Jensen and his collaborators[7] investigated the clinical effectiveness of the ester on a small group of patients with chronic pulmonary infection. The therapeutic results appeared to be supe-

rior to those obtained with benzyl penicillin. The increased sputum levels following the parenteral administration of diethylaminoethyl ester of penicillin in contrast to sodium penicillin was confirmed in England by Heathcote and Nassau[12] who also reported favorable results in the treatment of non-tuberculous bronchopulmonary infections. In preliminary reports by Barach rt al.,[13,3,4] a prompt and conspicuous improvement was observed in patients with chronic bronchitis and bronchiectasis as a result of intramuscular injections of the penicillin ester in doses of 1 to 2 million units daily for periods of six to 12 days.

Methods

During the past year, 80 patients received a total of 100 courses of the hydriodide salt of diethylaminoethyl ester of penicillin. Thirty-six in this series had bronchographic evidence of bronchiectasis. The remainder exhibited chronic bronchial or sino-bronchial infection associated with bronchial asthma and pulmonary emphysema. The patients selected for this study, the majority of whom had been followed for five years or more, presented clinical, bacteriologic and radiologic evidence which indicated or suggested chronic bronchitis, with or without chronic sinusitis. Twelve members of this group revealed the presence of chronic pneumonitis at the time treatment was instituted. Six were treated for acute upper respiratory infection which in the past had been a frequent cause underlying the exacerbation of their chronic pulmonary disease. Approximately half were hospitalized while the rest were treated as out-patients.

Prior to administering diethylaminoethyl iodide penicillin, studies in most instances included: (1) daily sputum volumes in hospitalized patients, (2) pus in sputum by gross appearance and microscopic examination, (3) culture of sputum specimens, (4) clinical evidence of infection, cough, wheezing, fever, malaise or weight loss, (5) roentgenograms of the chest. These studies were generally repeated during or after therapy. The duration of remission was evaluated in those patients who returned for follow-up examinations.

Pulmonary infection associated with bronchial asthma and pulmonary emphysema is prone to chronicity, marked by periodic acute exacerbations; this is particularly evident in cases with organic structural deterioration, such as in bronchiectasis and pulmonary fibrosis. The clinical evaluation, therefore, of any therapeutic regimen must be appraised in the light of these factors in the life cycle of chronic bronchopulmonary infection. The degree and duration of improvement were appraised objectively, in terms of cough, character and amount of expectoration, and the bacteriological analysis of the sputum. Additional factors such as weight gain, a reduction in asthma, relief of dyspnea, increase in exercise tolerance, and a sense of well-being were considered in the final assessment. In a number of cases, principally those patients in the bronchiectasis group, two to four repeated courses of neo-penil were administered. Respiratory function tests were followed in a few patients.

The diethylaminoethyl ester of penicillin was supplied as the hydroiodide

salt in the form of a dry, relatively insoluble powder which when reconstituted with sterile distilled water formed a milky suspension having a potency equivalent to 300,000 Oxford units of penicillin per cubic centimeter. The original material 1714-J Formula A, produced considerable foaming when reconstituted. This difficulty has been successfully overcome in the more recent material (Formula D). Neo-penil was administered intramuscularly once or twice daily in doses ranging from 500,000 to 2,000,000 units with average total dose of 9,000,000 units. The duration of therapy varied from three to 18 days, averaging approximately eight days for the 99 courses administered.

A total of 68 sputum specimens were assayed for their penicillin activity. The serial dilution tube method was employed with the Streptococcus hemolyticus strain C2O3 serving as the test organism. Thirty-three specimens were tested at varying collection periods ranging from two to 24 hours following a single dose of 500,000 units of neo-penil; 15 were assayed following the administration of 750,000 units; and 20 after 1,000,000 units.

Results

The clinical response of patients with chronic pulmonary infection is presented in Table I. Of 100 courses of neo-penil therapy, 81 resulted in a significant improvement, which was moderate in 27 and excellent in 55, in which a complete remission of the symptoms and physical signs of chronic suppuration was obtained; in 18 instances, little or no improvement occurred. It may be noteworthy that 10 of these were patients with long standing bronchiectasis who had for the most part failed to respond to other antibiotic and medical regimens. The most conspicuous results were obtained in cases of chronic suppurative bronchitis, with or without sinusitis. Cough and bronchospasm were markedly relieved or eliminated and the purulent character of the expectorate rendered mucoid in 47 of the 51 members of this group. The duration of remission averaged 8.0 weeks for the group as a whole.

Gross character of the sputum, smears and cultures were studied in 80 patients who received a total of 90 courses of neo-penil. In 90 instances, the sputum appeared purulent or mucopurulent, or pus cells were de-

TABLE I

CLINICAL EFFECT OF DIETHYLAMINOETHYL IODIDE PENICILLIN IN 80 PATIENTS WITH CHRONIC BRONCHOPULMONARY DISEASE

Diagnosis	No. of Courses	— — IMPROVEMENT — — Excellent	Moderate	Little or None
Chronic Bronchitis	51	30	17	4
Bronchiectasis	37	20	7	10
Chronic Pneumonitis	12	5	3	4
TOTAL	100	55	27	18

Duration of Remission: *Average*, 8.0 weeks; *Range*, 0.5 to 24.0 weeks.

monstrated on routine smear. Following therapy, sputum became mucoid in 55 instances. In four, expectoration was completely eliminated and no sputum was available for examination (Cf. Table II).

Of the 90 purulent specimens of sputum, 36 became sterile after treatment with neo-penil, as seen in Table III. In 27, gram positive organisms were eliminated with the emergence of gram negative bacilli, predominantly of the B. coli-aerogenes group. In three, yeast organisms of the monilia group were recovered. No change in bacterial flora occurred in 24 cases, with 14 revealing the persistence of hemolytic Staphylococcus aureus, coagulase positive, four B. Proteus, one pyocyaneus, five other organisms including Streptococcus viridans.

The penicillin levels in the sputum following the parenteral administration of neo-penil are illustrated in Table IV. Of the 33 specimens obtained after 500,000 units of neo-penil, five showed no detectable levels in eight, 12, or 24-hour collection periods. In 10 subjects, levels ranging from 0.02 units per cc. to 0.08 were obtained. In the remaining 18 patients levels in excess of 0.1 units per cc. were found, with one specimen as high as 1.5 units per cc. Of 15 patients given 750,000 units of neo-penil, 10 showed an average level of 0.055 units per cc. while five had an average of 0.2. In 19 subjects given 1,000,000 units the sputum concentration was between 0.2 and 0.48 units per cc. In this series there seemed to be no definitive correlation between the collection period and the levels obtained. The con-

TABLE II

EFFECT OF DIETHYLAMINOETHYL IODIDE PENICILLIN ON PERSISTENCE OF PUS IN SPUTUM IN 80 PATIENTS WITH BRONCHOPULMONARY INFECTION

No. of Courses	Sputum Examination*	Before	After Treatment
90	Purulent	50	12
	Muco-purulent	40	19
	Mucoid	0	55
	No sputum	0	4

*Presence of pus was determined by gross and microscopic examination of sputum.

TABLE III

EFFECT OF DIETHYLAMINOETHYL IODIDE PENICILLIN ON BACTERIAL FLORA OF SPUTUM IN 80 PATIENTS WITH BRONCHOPULMONARY INFECTION

	SPUTUM CULTURES CHANGED BY TREATMENT		
No. of Courses	Sterile	Gram-neg. Bacteria	Monilia
90	36	27	3

SPUTUM CULTURES UNCHANGED BY TREATMENT			
Staph. aureus	Proteus	Pyocyaneus	Other Organisms
14	4	1	5

centration of penicillin in the sputum generally varied with the dose of neo-penil administered. Other factors modify the penicillin content of the expectoration, such as the development of penicillinase during the period the sputum specimen is exposed to room air, but the results reported are those obtained with routine nurse to laboratory management.

In this group nine untoward reactions were encountered during the course of this study. Two consisted of a mild, transient urticaria. In two cases, a moderately severe rhinorrhea and bronchorrhea were attributed to the iodide radical of neo-penil; this factor also appeared implicated in two cases who manifested enlargement of the salivary glands 24 hours after injection. A systemic reaction, including a low grade fever, occurred in one subject. Syncope associated with bronchospasm and transient fall in blood pressure occurred immediately after the injection of neo-penil in a patient with bronchial asthma. Subsequently, this picture was reproduced in the same subject on re-exposure to the drug. There were two patients with a well-documented history of penicillin sensitivity who were able to tolerate neo-penil without allergic manifestations. On the other hand, swelling of the tongue and tachycardia occurred in one case during the third course; subsequently, a severe but transient asphyxial episode

TABLE IV

PENICILLIN CONCENTRATION IN SPUTUM FOLLOWING INTRAMUSCULAR INJECTION OF DIETHYLAMINOETHYL IODIDE PENICILLIN

GROUP I: *Sputum Level*, None (5 cases)

No. of Cases	Dosage (units)	Sputum Collection Period (hours)	Penicillin in Sputum (units per cc. average)
5	500,000	8 to 24	0

GROUP II: *Sputum Level, Slight*, 0.02 to 0.08 (21 cases)

No. of Cases	Dosage (units)	Sputum Collection Period (hours)	Penicillin in Sputum (units per cc. average)
10	500,000	8 to 24	0.05 to 0.07
10	750,000	12	0.05
1	1,000,000	48	0.07

GROUP III: *Sputum Level*, Moderate, 0.1 to 1.5 (42 cases)

No. of Cases	Dosage (units)	Sputum Collection Period (hours)	Penicillin in Sputum (units per cc. average)
14	500,000	12	0.35
4	500,000	8 to 24	0.25
5	750,000	12	0.2
6	1,000,000	12	0.2
7	1,000,000	2 to 4	0.32
5	1,000,000	28 to 48	0.48
1	1,000,000	48	0.48

with marked enlargement of the tongue took place in this patient after injection of 500,000 units penicillin-O intramuscularly.

The case histories of 10 patients are recited to portray the individual response to intramuscular injection of diethylaminoethyl iodide penicillin.*

Case 1: Female, age 55, had bronchial asthma from childhood. Since 1940 asthma became progressively more severe. Good clinical remissions were obtained at Presbyterian Hospital in 1943 with helium oxygen therapy; with bronchoscopic aspiration under ether anesthesia, in 1944 and 1951. During the previous eight years chronic low-grade fever, 99.0 to 101.0 degrees F. by mouth, persisted. Despite protracted coughing, she was unable to expectorate sputum. Nevertheless, during each bronchoscopy about 60 cc. of thick mucopurulent secretions were aspirated from the bronchi. A bronchogram did not reveal bronchiectasis; good filling of the bronchial tree was obtained, with the exception of most of the left lower lobe. On physical examination, the pharynx was reddened and lymphoid follicles were unusually prominent. Coarse rhonchi heard at the bases were accompanied by occasional crepitant rales at the left mid-lung field posteriorly.

Culture of bronchial aspirations revealed streptococcus viridans although pneumococcus organisms had been previously found on throat culture. Five-day courses of terramycin, 2 gms. daily, and chloromycetin, 2.5 gms. daily, had no effect on her febrile state nor on the complaint of soreness of the throat. The first course of diethylaminoethyl iodide penicillin, 800,000 units once daily for 14 days was followed by complete disappearance of fever and decreased redness of the pharynx. The lungs were clear. After an interval of one week, a second similar course for 10 days was followed by virtual clearing of the enlarged lymphoid follicles in the throat and disappearance of soreness of the throat.

Comment: A low-grade fever of eight years' duration was terminated as the result of administration of diethylaminoethyl iodide penicillin. A chronic bronchial and pharyngeal infection appears to have been eliminated since she has remained symptom-free, without cough, asthma or sore throat for one year. Among the striking features was the disappearance of the red swollen lymphoid follicles in the pharynx. This was thought to be of special interest in view of the high concentration that develops in lymph nodes following administration of diethylaminoethyl iodide penicillin. Although this patient manifested a surprising inability to expectorate, the complete absence of coughing for one year after treatment suggests a "cure" of chronic bronchitis.

Case 2: Female, age 58, had chronic persistent cough associated with many febrile episodes since childhood and consistently productive of purulent sputum which was often blood-streaked. Twenty years ago, following several episodes of pneumonitis, she was thought to have bronchiectasis; this was confirmed by lipiodol bronchography in 1941. Systemically administered penicillin produced some improvement in cough, but purulent quality of sputum was more decisively reduced by aerosol penicillin; the latter route of administration was discontinued because it produced wheezing. Terramycin, aureomycin and chloromycetin were each given in courses of five to seven days, 2.0 gms. daily, with marked symptomatic improvement but with recurrence five to 10 days later of purulent sputum and cough. In April, 1951, the positive physical findings were confined to the lungs, which revealed crepitant rales at the left base. An increase in lung markings was seen by x-ray film inspection over both lower lung fields, where a reticulated

*The case histories of five patients are included in the Journal; the remaining five histories will be in the authors' reprints.

appearance suggested bronchiectasis. Sedimentation rate and hemogram were normal. Sputum was purulent with staphylococcus viridans predominating.

One million units of diethylaminoethyl iodide penicillin were injected daily for nine days. On the fourth day of administration, the sputum became white and frothy, reduced from 3 ounces to ½ ounce daily. Repeated cultures at termination of this course showed the presence of N. catarrhalis with an occasional colony of B. coli. Another chest x-ray film revealed no significant change from the one taken before therapy. However, an excellent clinical remission continued for four months, with little cough and sputum remaining mucoid.

Recurrence of cough and purulent expectoration then took place, associated with acute laryngitis. Sputum culture showed the presence of streptococcus hemolyticus and staphylococcus aureus. She received 1,500,000 units of neo-penil daily for 10 days. By the third day sputum had again become white and mucoid, and cough was much improved. However, sputum began to turn purulent 10 days later, with recurrence of cough which increased considerably three months later. She was given a course of procaine penicillin, 1,200,000 units daily for seven days, without discernible clinical improvement; sputum continued to be yellow and purulent, with staphylococcus aureus on culture. Four days later, neo-penil, 1,000,000 units daily, was given for six days; sputum decreased in amount and became mucoid, with a rare colony of diplococcus pneumoniae on culture. Recurrence of gradually increasing cough and purulent sputum took place three weeks later. The organism isolated from the sputum was staphylococcus aureus. The patient, a school teacher, appeared to catch upper respiratory infections from contact with children. A course of terramycin, 2 gms. daily for five days, was now of no benefit. Chloromycetin, 3.0 gms. daily for eight days, resulted in a remission of cough and purulent sputum for three weeks. During a subsequent one week course of neo-penil, 1,000,000 units daily, purulent yellow sputum appeared, associated with increased cough and Friedlander B. on culture. Chloromycetin was administered again for five days with clearing of pus from sputum. A holiday at this time was followed by improvement in cough but reappearance of small amounts of pus in the sputum took place, with staphylococcus aureus present on culture.

Comment: Frequent courses of treatment with penicillin and the broad-spectrum antibiotics had been previously followed by temporary improvement in this patient with extensive bronchiectasis. The administration of diethylaminoethyl penicillin was at first accompanied by more decisive clearing of purulent sputum and more lasting remission than the other antibiotics employed. Elimination of the chronic bronchial infection, due to staphylococcus aureus, was not achieved. Following one of the courses of neo-penil, abrupt cessation of improvement was associated with presence of B. Friedlander in the sputum; at this time, chloromycetin was markedly effective.

This patient illustrates the frequency with which staphylococcus organisms develop resistance to penicillin and other antibiotics. During the last winter exposure to children with upper respiratory infection was apparently a factor in the recurrent exacerbations of infection which she manifested. New measures, such as sleeping with the heat down 16 degrees and bacterial vaccines, will be tried in the attempt to reduce the need for antibiotics in the coming term.

Case 3: Female, age 38, had bronchial asthma for 10 years, initially treated in 1942 at the Allergy Clinic, where she was found to be sensitive to house dust, ragweed and feathers. She was treated with hyposensitization and remained under

fair control until 1944, when she had an increase in cough and sputum. A low-grade fever persisted for four weeks, following which she had a remission from asthma until 1947. After an upper respiratory infection, asthma recurred, accompanied by severe cough and copious, purulent sputum. In six months a weight loss of 20 pounds took place. With elevation in temperature to 103 degrees F. she was admitted to Presbyterian Hospital in July, 1948.

Except for bilateral wheezes, the lungs appeared clear. An x-ray film of the chest disclosed evidence of atypical pneumonia of the right upper lung field. This failed to respond to penicillin therapy but resolved spontaneously by lysis in two weeks.

Since discharge from the hospital she continued to suffer from chronic protracted asthma associated with severe coughing and expectoration of purulent sputum, approximately 400 cc. daily. During a period of three years her sputum remained purulent most of the time, with cultures consistently revealing the presence of hemolytic staphylococcus aureus, at times hemolytic streptococcus and, on occasions, K. pneumoniae. Many courses of the broad-spectrum antibiotics resulted in little if any improvement; inhalation of penicillin and streptomycin aerosols temporarily cleared the infection but increased her bronchospasm. Following a short course of cortisone, she had a partial remission from asthma which lasted one month. In June, 1951, an upper respiratory infection, accompanied by chills and fever, was followed by exacerbation of asthma and expectoration of increased amounts of thick, yellowish sputum. Despite chloromycetin and aureomycin therapy, severe asthma persisted, necessitating hospitalization in November of 1951. She was given 1,000,000 units of neo-penil twice daily for eight days after which the sputum became scanty and colorless; asthma and cough completely subsided. This remission was of six weeks' duration when another upper respiratory infection produced a relapse and sputum again became purulent. She was placed on 2,000,000 units of crysticillin (procaine penicillin) for eight days, which resulted in a partial remission, with the sputum again becoming mucoid, which lasted only 14 days. The administration of neo-penil appeared to be more effective than procaine penicillin, in respect to promptness of relief of infection and subsequent duration of benefit.

Comment: Recurring bronchopulmonary infection, with staphylococcus aureus apparently the significant etiological agent, was not controlled by the broad-spectrum antibiotics employed in this patient. The disappearance of pus from the sputum after administration of diethylaminoethyl iodide penicillin was accompanied by complete disappearance of cough and asthma. More prolonged therapy would appear to be indicated in cases of this type in the attempt to produce more lasting remissions. Following elimination of purulent sputum, after intramuscular injections of this drug, penicillin by mouth in large dosage, one million units on arising and one to two million units on retiring, seems to be a feasible method of continued treatment which deserves further trial.

Case 4: Male, age 65, had chronic cough and shortness of breath of 15 years' duration, increasing in severity during the past three years. In January, 1951, wheezing on slight effort and expectoration of purulent sputum became evident. The positive findings were restricted to the chest, which was emphysematous, with distant breath sounds and high pitched expiratory wheezes heard bilaterally. A vital capacity of 2,700 cc. rose to 3,400 cc. after inhalation of vaponefrin. Sputum showed pus, with staphylococcus aureus and diplococcus pneumoniae on culture. Chest x-ray film revealed an increase in the bronchovascular markings and findings consistent with pulmonary emphysema.

Courses of penicillin by injection, aureomycin and chloromycetin by mouth were

employed in the treatment of his bronchopulmonary infection, with moderate benefit in cough and gradual clearing of purulent sputum. In October, 1951, during an episode of acute respiratory insufficiency following increased infection, he was admitted to Presbyterian Hospital. At this time, examination of the lungs disclosed many wheezes with marked prolongation of the expiratory phase. The diaphragms were immobile, respiration was labored and upper costal. Erythroyte sedimentation rate was 23 mm. per hour. Venous pressure was 48 mm. H_2O; temperature, 101 degrees F. Sputum was purulent, with staphylococcus aureus found on culture. He was placed on neo-penil, 1,000,000 units daily for six days. Decrease in cough, with sputum scanty and mucoid, was observed on the fourth day of treatment. Temperature dropped to normal in 48 hours and all evidence of bronchospasm cleared. This remission in cough and dyspnea was largely maintained for three months. In a follow-up four months later, moderate cough had recurred, but the expectoration was mucoid, and bronchospasm minimal.

Comment: A prompt clearing of bronchopulmonary infection took place in this patient with chronic bronchitis following the use of neo-penil, one million units daily, for six days, with striking associated improvement in cough and bronchospasm. Staphylococcus aureus was the organism found on sputum culture. The importance of effective elimination of bronchial infection in patients with pulmonary emphysema was illustrated by the course of this patient. The persistence of improvement was surprising in view of the relatively short period of treatment.

Case 5: Female, age 41, had allergic vasomotor rhinitis and polyposis since 1931. In 1947 asthma began, but controlled by a hyposensitization program until 1950 when she was hospitalized on four occasions for status asthma. During the last admission she received 100 mgs. ACTH daily for five days which resulted in a remission lasting 29 days. Asthma gradually recurred and in March, 1951, a siege of severe bronchospasm was treated with cortisone, which resulted in a complete remission for six months, when she was given a second course of cortisone which resulted in a partial remission, aided by bronchodilator medication daily.

In January, 1952, following an upper respiratory infection, her sputum became thick and purulent, with diplococcus pneumoniae present on culture. Severe asthma necessitated use of helium and oxygen, and intravenous aminophyllin. She was given 1,000,000 units neo-penil daily for five days with an excellent symptomatic response, a remission of two months' duration. Sputum culture after neo-penil therapy was sterile. In March, 1952, her asthma again increased in severity after another upper respiratory infection. Sulfonamides were given without benefit. After another course of neo-penil, 1,000,000 units per day for six days, a remarkable improvement in asthma took place, accompanied by a decrease in sputum which changed from purulent to mucoid in character. This improvement has persisted for the past two months.

Comment: A prompt control of a pneumococcus respiratory infection, achieved by six days of neo-penil, one million units daily, was accompanied by a striking improvement of bronchial asthma. The response of patients with bronchial asthma to antibiotic therapy is especially favorable only in those cases in which the sputum is frankly purulent, either on inspection or on microscopic examination.

Both the effectiveness of clearing of pus from the sputum as well as the promptness with which improvement was manifested suggested that this drug had a beneficial effect superior to that of benzylpenicillin, and

comparable, in many instances, to the action of inhalation of penicillin as an aerosol. Although three cases were encountered in which inhalation of penicillin resulted in disappearance of purulent sputum due to a resistant Staphylococcus aureus, when previous treatment with neo-penil appeared to be less effective, the majority of cases with suppurative bronchopulmonary disease were considered markedly benefited. This opinion, largely based on a previous clinical experience of the two senior authors in this report, must admittedly be accepted as suggestive evidence rather than demonstrable proof. The well-known difficulty of predicting in advance the reaction of a patient with bronchopulmonary disease to antibiotic treatment is admitted; nor does the in vitro sensitivity of the organisms to penicillin and other agents always contribute a decisive aid in this respect. In three patients in whom a B. proteus infection had taken place following elimination of both gram positive and gram negative organisms by multiple antibiotic therapy, the employment of neo-penil in dosages of 1,000,000 units twice daily for eight to 12 days was accompanied by a marked reduction in cough and disappearance of expectoration; the sputum was mucoid instead of purulent, despite the fact that the B. proteus organism had been repeatedly found to be resistant to penicillin in vitro sensitivity tests. Later, a second course of benzyl procaine penicillin in the same dosage was followed by a similar striking improvement in two of these cases.

Pharmacologic evidence for a specific favorable effect of neo-penil in lung infections is found in the presence of penicillin in the sputum in higher concentrations than that which has been reported following injection of benzylpenicillin. In the study of Humphrey and Joules[4] penicillin was rarely found in the sputum in cases of bronchitis and bronchiectasis after its intramuscular injection; whereas in patients with lobar pneumonia small amounts of penicillin were recovered from the sputum during the active phase of the disease. When the consolidation cleared and a chronic bronchitis persisted no penicillin could be detected after intramuscular injection of penicillin, even though patients continued to have considerable amounts of expectoration. In the studies of Barach et al.,[15,16] Bobrowitz, Edwin et al.,[17] penicillin was rarely found in the sputum after intramuscular injection. On the other hand, in 42 of 68 cases of this series in which sputum concentration was tested after 500,000 units to 1,000,000 units of neo-penil, a level between 0.1 and 1.5 units per cc. of sputum was present. These results confirmed the observation made by Jensen et al. and Heathcote and Nassau in which higher concentrations of penicillin in the expectoration were apparent after the injection of diethylaminoethyl iodide penicillin than after the introduction of comparable amounts of benzyl-penicillin. Although aerosol penicillin results in far higher penicillin concentrations, 50 to 1,000 units of penicillin per cc. of expectoration,[14-18] the demonstration that penicillin is present in bronchial secretions in the majority of cases in a concentration that would be expected to inhibit the growth of gram positive bacteria, except highly resistant Staphylococcus aureus, appears to offer a sound bacteriologically based

argument for the superiority of neo-penil over procaine penicillin in cases of bronchopulmonary suppuration.

The effect of diethylaminoethyl iodide penicillin on the bacterial flora of the sputum indicated the effectiveness of the preparation in patients with chronic bronchitis and bronchiectasis. Of 90 courses of treatment the sputum cultures were sterile in 36. In 27 other cases, only gram negative bacteria were recovered on culture. This finding is to be interpreted as a sign of the potency of the preparation against infection with gram positive micro-organisms, as originally pointed out in the use of aerosol penicillin in cases of this type.[19] Although the broad spectrum antibiotics were found highly valuable for treatment of secondary infections with gram negative bacteria, and for acute respiratory infections, their long-continued employment to obtain an arrest of chronic respiratory infection required certain precautions to avoid the development of invasion with unusual organisms such as B. proteus, B. pyocyaneus, and Monilia. The special considerations involved in the therapy of chronic bronchopulmonary infections have been recently described.[3,4]

The clinical indications for the use of diethylaminoethyl iodide penicillin include the majority of cases of chronic bronchitis, bronchiectasis and chronic pneumonitis. Effective treatment over a period of six to 12 days may be initiated for exacerbations of chronic respiratory infection, or preoperative and postoperative treatment of bronchiectasis and as a beginning of more long-continued treatment of chronic bronchiectasis and bronchitis. After 12 days of intramuscular injection the attempt to initiate a long-continued arrest of infection may be continued with aerosol penicillin or with penicillin by mouth in larger dosages than had previously been used. In our clinic it has recently been found clinically valuable to give 1,000,000 units of penicillin or arising and 1,000,000 units, at times 2,000,000 units, at night for a period of three weeks to three months or more in the attempt to maintain the patient free from the symptoms and signs of chronic infection. The latter method of administration is altered in those cases in which resistant Staphylococcus aureus organisms appear and are responsible for return of a purulent quality of the sputum. In this event, recourse may be had to inhalation of 600,000 to 1,000,000 units of penicillin daily by aerosol, aureomycin or terramycin, generally administered for periods of five to eight days.

It would also appear reasonable to sanction the employment of diethylaminoethyl iodide penicillin in upper respiratory infections, pharyngeal, sinus and bronchial infection that follow in the wake of the common cold. In patients with infection of the cervical (or other) lymph glands, neopenil would appear to be especially effective, as suggested by a remarkably favorable response in two such cases in this series. In patients with chronic infection of the respiratory tract, neo-penil as well as other antibiotic therapy is more apt to be followed by prolonged benefit if adequate bronchial and bronchiolar drainage is accomplished. Among the measures that are therapeutically feasible and effective for this purpose are: use of the head-down position, training in diaphragmatic breathing, deliberate cough-

ing after inhalation of broncho-dilator aerosols, manual compression of the abdomen and lower chest, as well as the employment of recently developed physical methods of eliminating bronchial secretions. The portable Exsufflator with a negative pressure attachment,[20] has in some cases been found more efficient in eliminating retained secretions from the smaller bronchi than the natural cough of patients with pulmonary emphysema and bronchial asthma.*

SUMMARY

The clinical results of the use of diethylaminoethyl ester hydroidide of penicillin G are reported in 80 patients with chronic bronchopulmonary disease, including chronic bronchitis, bronchiectasis and chronic pneumonitis. Of 100 courses of treatment, an excellent result was obtained in 55, moderate improvement in 27 and little or no benefit in 18.

Of 90 courses in which the sputum was purulent or mucopurulent before treatment, the result after treatment was no sputum in four instances, mucoid in 55, mucopurulent in 19 and purulent in 12. The sputum cultures after treatment were as follows: sterile in 36, gram negative bacteria in 27; Staphylococcus aureus in 14, B. proteus in four, pyocyaneus in one, yeast organisms in three, other organisms, including Streptococcus viridans, in five.

The penicillin concentration of the sputum tested after intramuscular injection of 500,000 to 1,000,000 units of neo-penil, varied between 0.1 and 1.5 units per cc. in 48 of 68 instances. In 19 cases the penicillin level in the sputum after 1,000,000 units was between 0.2 and 0.48 units per cc.

The case histories of patients with bronchopulmonary infections illustrate the effect of this drug on the course of their disease.

The clinical and bacteriological observations made on the use of diethylaminoethyl iodide penicillin in patients with chronic bronchitis, bronchiectasis and chronic pneumonitis suggest that this agent has a markedly effective action in the control of infections due to gram positive organisms. The side effects of the drug have not been of such severity or frequency as to limit its employment; allergic reactions to penicillin and the consequences of iodine sensitivity were among those encountered.

RESUMEN

Se refieren los resultados del uso del ester de yodihidrato de dietilaminoetil penicilina G en 80 enfermos con padecimientos broncopulmonares crónicos, incluyendo bronquitis crónica, bronquiectasia y neumonitis crónica. De 100 series de tratamiento se obtuvo un excelente resultado en 55, mejoría moderada en 27 y beneficio escaso o ninguno en 18.

En 90 series, en las que el esputo era purulento antes del tratamiento, el resultado después del tratamiento fué: ausencia de esputos en 4 casos,

*Deliberate coughing may be most productive after broncho-dilation has been accomplished by drugs such as aminophylline, grains 5, especially when combined with benzocaine, grains ½, as an anti-nausea factor, and inhalation of epinephrine compounds, including 2.25 per cent racemic epinephrine, nebulized with a handbulb, or in dilute solution with pressure-breathing apparatus.

mucoide en 55, mucopurulento en 19 y purulento en 12. Los cultivos del esputo después del tratamiento resultaron: Esteriles 36; con bacterias Gram-negativas en 27; Estafilococo áureo en 14; Bacteria proteus en 4; piocianico en 1; micro-organismos de tipo levadura en 3, y otros micro-organismos, incluyendo estreptococo viridans en 5.

La concentración de la penicilina en el esputo después de inyectar 500,000 a 1,000,000 de unidades de Neo-penil, varió entre 0.1 y 1.5 unidades por cc. en 48 de 68 casos. En 19 casos el nivel de la penicilina en el esputo después de 1,000,000 unidades fué entre 0.2 y 0.48 unidades por cc.

Las historias clínicas de los enfermos con afecciones broncopulmonares son ilustrativas del efecto de esta droga sobre el curso de la enfermedad.

Las observaciones clínicas y bacteriológicas hechas sobre el uso del yodhidrato del dietilaminoetyl penicilina, en enfermos con bronquitis crónica, bronquiectasia, y neumonitis crónica, sugieren que este agente tiene una acción marcada y efectiva en el dominio de las infecciones causadas por gérmenes Gram-positivos. Los efectos colaterales al uso de la droga no han sido de una severidad tal que limite su uso fueron observadas reacciones alergicas a la penicilina y consecuencias de la sensibilidad al yodo como algunos de los efectos colaterales.

RESUME

Les auteurs rapportent les résultats cliniques de l'utilisation du diethylaminoethyl-ester-hydroiodide de pénicilline G chez 80 malades atteints d'affections bronchopulmonaires chroniques, comprenant bronchites chroniques, dilatations bronchiques, et pneumonies chroniques. Sur 100 malades mis en traitement, on peut noter 55 excellents résultats, 27 améliorations modérées, et 18 cas dont l'amélioration fut très discrète ou même non perceptible.

Sur 90 cas, dans lesquels l'expectoration était, avant traitement, purulente ou mucopurulente, on observa les résultats suivants après traitement: 4 cas où il n'y avait plus aucune expectoration; 55 cas où l'expectoration était devenue mucoïde, 19 chez lesquels elle était devenue mucopurulente, et 12 chez lesquels l'expectoration était restée purulente. Après traitement, la culture des crachats donna les résultats suivants: absence de germes dans 36 cas, présence de bactéries gram-négatif dans 27 cas, staphylocoques dorés dans 14 cas, proteus dans 4 cas, pyocyaniques dans un cas, des levures dans trois cas, et d'autres microbes, y compris le streptocoque viridans dans 5 cas.

La concentration de pénicilline dans les crachats, évaluée après injection intra-musculaire de 500,000 à un million d'unités de néo-pénil varia dans 48 cas sur 68 de 0.1 à 1.5 unité par cc. Dans 19 cas, le niveau de pénicilline des crachats après l'administration d'un million d'unités se situa entre 0.2 et 0.48 unité par cc.

Les observations des malades atteints d'affections broncho-pulmonaires démontrent l'action de cette drogue sur l'évolution de leur affection. Les observations cliniques et bactériologiques qui ont été faites sur l'usage du produit chez des malades atteints de bronchite chronique, de dilatation des

bronches, et de pneumonie chronique amènent à penser qu'il a une action particulièrement efficace sur les affections dues au germes gram-positif. Cette médication ne semble pas avoir d'inconvénients dont la gravité ou la fréquence puisse limiter son utilisation. Parmiceux qui furent rencontrés, il faut citer les réactions allergiques à la pénicilline, et les conséquences de la sensibilisation à l'iode.

REFERENCES

1 Castex, M. R., Capdehourat, E. I. and Laverello, A.: "Nuevo tratamiento de las supuraciones bronchopulmonares; accion curativa de un preparado sulfamidico nebulizada," *Rev. Asoc. med. argent.*, 55:85, 1941.

2 Barach, A. L.: "Physiologic Therapy in Respiratory Disease," Lippincott Co., Philadelphia, 1948.

3 Barach, A. L., Bickerman, H. A. and Beck, G. J.: "Advances in the Treatment of Non-tuberculous Pulmonary Disease," *Bull. N. Y. Acad. Med.*, 28:353, 1952.

4 Barach, A. L. and Bickerman, H. A.: "Antibiotic Therapy in Bronchiectasis, Chronic Bronchitis, Bronchial Asthma and Pulmonary Emphysema; The Use of Penicillin, Especially by Inhalation, and Aureomycin, Terramycin and Chloromycetin," *Arch. Int. Med.* (In press).

5 Jensen, K. A., Dragsted, P. J. and Kiaer, I.: "Undersogelser af penicillin-praeparater of doeringsmader II," (Investigations of Penicillin Preparations and Dosage), *Ugeskr. laeger.*, 112:1075, 1950.

6 Jensen, K. A., Dragsted, P. J., Kiaer, I., E. Juhl Nielsen and Frederiksen, E.: "Leocillin" (benzyl penicillin-B-diethylaminoethylester hydrojodid). Leocillin (benzyl penicillin-B-diethylaminoethylester hydriodide), *Ugeskr. laeger*, 113: 1035, 1951.

7 Jensen, K. A., Dragsted, P. J. and Kiaer, I.: "Undersogelser over leocillinate terapeutiske virkning" (Investigation of the therapeutic effect of leocillin)," *Ugeskr. laeger.*, 113:1039, 1951.

8 Meyer, K., Hobby, G. L. and Chaffee, E.: "On Esters of Penicillin," *Science*, 97: 205, 1943.

9 Meyer, K., Hobby, G. L. and Dawson, M. H.: "The Chemotherapeutic Effect of Esters of Penicillin," *Proc. Soc. Exper. Biol. and Med.*, 53:100, 1943.

10 Richardson, A. P., Walker, H. A., Miller, I. and Hansen, R.: "Metabolism of Methyl and Benzyl Esters of Penicillin by Different Species," *Proc. Soc. Exper. Biol. and Med.*, 60:272, 1945.

11 Carpenter, F. H.: "The Anhydride of Benzylpenicillin," *J. Am. Chem. Soc.*, 70: 2964, 1948.

12 Heathcote, A. G. S. and Nassau, E.: "Concentration of Penicillin in the Lungs. Effects of Two Penicillin Esters in Chronic Pulmonary Infections," *Lancet*, 1: 1255, 1951.

13 Barach, A. L.: "Remissions in Bronchial Asthma and Pulmonary Emphysema," *J.A.M.A.*, 147:730, 1951.

14 Humphrey, J. H. and Joules, H.: "Penicillin Inhalation in Pulmonary Disease," *Lancet*, 2:221, 1946.

15 Garthwaite, B. and Barach, A. L.: "Penicillin Aerosol Therapy in Bronchiectasis, Lung Abscess and Chronic Bronchitis," *Am. J. Med.*, 3:261, 1947.

16 Barach, A. L., Bickerman, H. A. and Garthwaite, B.: "Studies on Aerosol Deposition," *Post-Graduate Med.*, 5:314, 1949.

17 Bobrowitz, F. D., Edlin, J. S., Bossin, S. and Wolley, J. S.: "Penicillin in Treatment of Bronchiectasis; Preliminary Report," *New England J. Med.*, 234:141, 1946.

18 Segal, M. S., Levinson, L. and Miller, D.: "Penicillin Inhalation Therapy in Respiratory Infections," *J.A.M.A.*, 134:762, 1947.

19 Barach, A. L., Silberstein, F. H., Oppenheimer, E. T., Hunter, T. and Soroka, M.: "Inhalation of Penicillin Aerosol in Patients with Bronchial Asthma, Chronic Bronchitis, Bronchiectasis and Lung Abscess; Preliminary Report," *Ann. Int. Med.*, 22:4, 1945.

20 Barach, A. L. and Beck, G. J. with Smith, W. H.: "The Principles and Technic of Operation of the Exsufflator," *Am. Pract. and Dig. of Treatment*, 3:733, 1952.

The Use of Neo-Penil, a Diethylaminoethyl-Ester of Penicillin, in Pulmonary Disease*

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Following Jensen's[1] pilot studies, neo-penil was introduced in this country for laboratory and clinical evaluation and several groups of investigators have been working on this subject. Jensen demonstrated that neo-penil concentrations in the lung tissue were five to 10 times higher than those obtained by equal doses of sodium or procaine penicillin injected intramuscularly. These studies were subsequently confirmed and effective concentrations of neo-penil in the sputum were found by Heathcote and Nassau in England.[2] Pharmacologic experiments demonstrated that neo-penil, although somewhat more toxic than procaine penicillin, was well tolerated even in large doses.[3] Barach and his associates subsequently observed prompt elimination of pus from the sputum in 75 per cent of a group of 50 patients with chronic bronchitis and bronchiectasis, with comparable clinical improvement. They considered neo-penil of unique value in respiratory infections due to gram-positive bacteria.[4]

Because of the large incidence and the serious significance of resistant infectious nidi in chronic lung diseases, we were impressed by the possibilities that this new preparation offered. Our interest has centered primarily about the clinical usefulness of this preparation. We have also carried out careful biological assays in a small group of patients. The studies were performed primarily at the Boston City Hospital. An additional group of patients were followed by Dr. Bueno at St. Anne's Hospital in Fall River, Mass., and results in five tuberculous patients were also recorded following personal communication from Dr. G. Sayago in Argentina.

Present Studies

Our observations were made in 48 patients, all but one of them suffering from acute or chronic pulmonary diseases. Since the majority had multiple diagnoses, we decided to classify them according to the primary disease at the time of hospitalization. Some, following discharge, continued to have neo-penil at home. Evaluation of the results is difficult, for as with other antibiotics, clinical and experimental observations should be confirmed in a statistically larger number of patients before definite conclusions can be made. We selected, therefore, to observe certain objective changes, such as temperature, amount of expectoration, intensity and character of the cough, variation of the bacterial flora, and roentgenographic changes, along with the patients' subjective impressions.

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Several patients had received procaine or regular penicillin before neo-penil was started. Certain differences in response to these preparations were noted in this group. Fortuitously, these patients could serve somewhat as controls. Unfortunately, it is impossible to appraise the difference in behavior between these two drugs in the same patient, unless the same pathological conditions can be reproduced.

Diagnosis: The group of patients studied comprised: ten with chronic bronchial asthma and pulmonary infection;[5] nine with lobar pneumonia; six with acute and chronic bronchitis; five with pneumonitis; four with chronic pulmonary emphysema; four with bronchiectasis; four with bronchopneumonia; and one each with tuberculosis,* sialolithiasis, bilateral maxillary sinusitis, acute pleurisy, pneumoconiosis, and atelectasis.

Age: Most of the patients were adults in their middle age, although some children were also included. The general age ranged from 6 months to 77 years.

Doses: We started using rather high doses, but in the course of study, it became apparent that for most of the patients, total (divided) doses of 500,000 to 1,000,000 units daily would suffice. In general, we employed daily doses ranging from 300,000 units (once) to 500,000 units every six hours, without any detectable untoward effects. The total dose for a complete course of treatment ranged from 2,100,000 units given in five days to 24,000,000 units administered over a 12 day period.

Results

I. *Biological Assay:*

The blood and sputum levels in six patients were carefully studied following the administration of single intramuscular doses of neo-penil.

The bloods were drawn under sterile precautions and the serum assayed for penicillin levels. The sputum was not allowed to stand at the patient's bedside. It was taken immediately to the laboratory where the following procedure was employed: (1) homogenization in a blender for 15 minutes; (2) centrifuging for 15 minutes; (3) running the supernatant portion of the sputum through sterile fritted ultra-fine glass filter into sterile side-arm flask, using suction. After the sputum was thus sterilized, it was assayed by the Rammelkamp[6] serial dilution method for both the blood and sputum, using pure cultures of Sarcina lutea.

Following single intramuscular doses of 300,000; 500,000; and 1,000,000 units of neo-penil, four-hour peak levels were determined in the blood and sputum. The blood peak levels ranged from 0.1 to 1.1 units per cc. The sputum peak levels, in the same patients, ranged from 0.35 to 3.0 units of penicillin per cc. (Figure 1).

Clinical Results:

A) *Temperature:* The temperature became normal in all the cases except six, of whom four were not treated further with any other antibiotics and yet continued to improve steadily. The remaining two were unaffected

*Five additional cases were observed by Dr. Sayago.

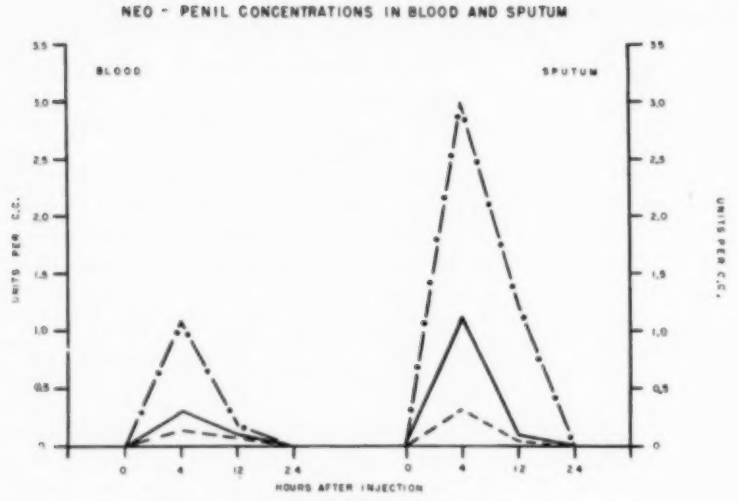

FIGURE 1

— — — — Average of Three Patients: 300,000 units (single dose) I.M.
———— Average of Six Patients: 500,000 units (single dose) I.M.
——. ——. Average of Three Patients: 1,000,000 units (single dose) I.M.

by subsequent treatment with other antibiotics. No definite pattern of temperature drop could be detected during treatment. Defervescence appeared mostly related to the characteristics of the particular disease.

B) *Expectoration:* The daily amount of expectoration in each patient was significantly decreased in all but three. This beneficial result was supplemented by the change in the character of the sputum which became less purulent in those with bronchiectasis. Another observation, worthy of further investigation, was the fact that many of the asthmatic patients stated that it was easier for them to raise their sputum.

C) *Cough:* The cough was uniformly decreased in all the patients, and this significant finding correlated well with the changes in expectoration. Again, the hard, troublesome, hacking type of cough, especially in the bronchial asthma patient, was usually relieved.

D) *Bacterial Flora:* In general, the effect of neo-penil upon the change of bacterial flora in the sputum did not appear to correlate with the rest of the findings. Some bacteria, like Alpha streptococcus, Neisseria flavus, and Neisseria catarrhalis, were usually unaffected by the drug, remaining at the end of treatment. In some cases, these organisms appeared after completion of treatment without having been present at the start. Pneumococci, mostly of type 6, invariably disappeared after treatment. Staphylococcus albus and aureus were also mostly inhibited, while persistence of Hemophilus influenzae strains were noted in one half of the cases upon completion of treatment. Bacillus proteus was consistently unaffected by neo-penil.

The emergence of pathogenic and non-pathogenic organisms that were not present in the beginning but were present at the end of treatment merits consideration. In our studies such organisms were noted frequently; however, their presence appeared to have no appreciable effect on the clinical course of the disease. In order of frequency, the following new bacteria were recovered from the sputum at the end of treatment: Bacillus pyocyaneus, Bacillus proteus, Neisseria catarrhalis, Monilia albicans, diphtheroids, Aerobacter aerogenes, and Eschericha coli. These organisms are more or less unaffected by penicillin. The significance of the change of bacterial flora resulting from antibiotic therapy has been commented on, and caution against the indiscriminate use of antibiotics has been stressed by many investigators.[7-10] This change, however, has been noted with practically all of the antibiotics and appears to be higher with the use of the broad spectrum antibiotics.

E) *Side Effects:* No significant toxic or untoward effects were noted during or after neo-penil treatment. One patient developed a transient skin rash that was promptly overcome by the use of antihistaminics. The rash was probably due to a penicillin idiosyncrasy, inasmuch as the same reaction occurred one year previously when procaine penicillin was employed.

TABLE I

DIAGNOSIS AND CLINICAL RESULTS

DIAGNOSIS	RESULTS			
	No Therapeutic Effects	Fair	Good	Excellent
Bronchial Asthma	1	4	5	
Acute and Chronic Bronchitis			4	2
Emphysema	2	1	1	
Bronchiectasis		2	2	1
Tuberculosis*	1			
Pneumonitis	2	1	2	
Pneumonia (Lobar)		3	1	5
Sialolithiasis				1
Sinusitis				1
Bronchopneumonia (Acute)			3	1
Pleurisy			1	
Pneumoconiosis	1	1		
Atelectasis			1	

*Defervescence was noted in five additional tuberculous patients, whose temperatures could not be controlled by streptomycin or isonicotinic acid hydrazide and were successfully treated with neo-penil.

The results, taking into consideration all the factors mentioned above, were classified as follows:

TABLE II
SUMMARY — RESULTS

No Therapeutic Effect	8
Partial Relief of Symptoms and Slow Improvement in X-ray Films	9
Good	22
Excellent	9

Discussion

It is quite difficult to state the benefits of an antibiotic that has been used in a variety of diseases in some of which the infectious component played only a part. Furthermore, most of the patients had multiple diagnoses and were in rather poor general condition. All of those with penicillin-sensitive organisms showed definite improvement, and the degree of that improvement was mainly related to the particular characteristics of each disease. It can be stated that neo-penil represents an agent as good as procaine penicillin, plus the potential advantages of producing much higher tissue levels. This fact must be taken into consideration very seriously, for a bacteriostatic action may be transformed into a bactericidal one upon the achievement of high levels in the diseased organ. This led us, in the later stages of the present study, to recommend the use of smaller doses of neo-penil. There were no changes in the final results, and, therefore, for all practical purposes we believe the dosage can be standardized on the same basis as procaine penicillin.

Relative effectiveness of neo-penil, as compared to procaine penicillin, is most difficult to decide. In this series there were seven patients who had received regular or procaine penicillin prior to neo-penil without appreciable improvement, and yet responded favorably to the latter. Absolute conclusions cannot be drawn from such a small number of patients. It appears reasonable that the higher local deposit of neo-penil was the responsible factor for this improvement. This was further confirmed in one patient who had sialolithiasis and was unsuccessfully treated with 600,000 units daily of procaine penicillin for one week. After two days of treatment with neo-penil with doses of 250,000 units twice daily, all the inflammatory and congestive changes subsided, and the surgeon was able to remove the stone without difficulty. We present this case because it permits a clinical, as well as pathological, appraisal of the effects of neo-penil on a visible organ. This cannot be carried out with equal accuracy in pulmonary or other internal diseases.

Acknowledgment: The authors wish to acknowledge the technical assistance of Miss Doris Grossman in carrying out the penicillin biological assays.

SUMMARY

1) Clinical studies and biological assays of a new penicillin preparation (Diethylaminoethyl-ester-hydroiodide) were carried out in patients with pulmonary diseases.

2) Clinical results were encouraging and mostly evident in the relief of cough, the decrease and change in character of the expectoration and control of temperature.

3) Penicillin sputum peak levels were consistently much higher than those obtained in the blood serum.

4) The conversion of bacterial flora lagged behind the clinical results. The appearance at the end of treatment of new bacterial flora, though frequent, did not alter the beneficial clinical results.

5) Neo-penil appeared to be an effective penicillin preparation for pulmonary diseases, whenever a higher local concentration of the drug in the diseased lung was desired.

RESUMEN

1) Fueron llevados a cabo, en pacientes con enfermedades pulmonares, una serie de estudios clinicos y ensayos biologicos de un nuevo preparado de penicilina (Ester del yodhidrato de dietil amino etil).

2) Los resultados clinicos fueron alentadores y especialmente evidentes en el alivio de la tos, la disminución y cambio de aspecto de la expectoración y en el control de la temperatura.

3) Las concentraciones máximas de penicilina en el esputo, fueron ostensiblemente mayores que las obtenidas en el suero sanguineo.

4) La conversión de la flora bacteriana se efectuó tardiamente en relación a los resultados clinicos. Al final del tratamiento fué frecuente la aparición de una nueva flora bacteriana, pero no altero los buenos resultados clinicos.

5) El Neo-Penil demostró ser un eficaz preparado de penicilina en el tratamiento de las enfermedades pulmonares, especialmente cuando son necesarias elevadas concentraciones de la droga en el pulmón enfermo.

RESUME

1) Les auteurs ont poursuivi des études cliniques et des épreuves biologiques chez des malades atteints d'affections pulmonaires, avec une nouvelle préparation de pénicilline (diethylaminoethyl-ester-hydroiodide).

2) Les résultats cliniques se montrèrent encourageants, et généralement évidents dans le soulagement de la toux, la diminution et les modifications des caractères de l'expectoration, et la chute thermique.

3) Le taux de pénicilline des crachats s'éleva à des niveaux constamment beaucoup plus hauts que ceux obtenus dans le sérum sanguin.

4) Les résultats cliniques dépassèrent largement les résultats bactériologiques donnés par l'étude de la flore des crachats. A la fin du traitement, l'apparition fréquente d'une nouvelle flore bactérienne ne modifia pas les heureux résultats cliniques.

5) Le néopénil a semblé être une préparation de pénicilline efficace dans les affections pulmonaires chaque fois que l'on désirait obtenir une concentration élevée du produit dans le poumon malade.

REFERENCES

1 Jensen, K. A., Dragsted, P. J., Moler, P. and Klaer, I.: "Investigations of Penicillin Preparations and Dosage Schedules," *Ugeskrift Laeg.*, 112:1043, 1950.

2 Heathcote, A. G. S. and Nassau, F.: "Concentration of Penicillin in the Lungs," *The Lancet*, 1:1255, 1951.
3 Smith, Kline and French Laboratories: Personal communication.
4 Barach, A. L.: "Remissions in Bronchial Asthma and Hypertrophic Pulmonary Emphysema," *J.A.M.A.*, 147:730, 1951.
5 Segal, M. S., Dulfano, M. J. and Herschfus, J. A.: "Recent Advances in the Physiology and Treatment of Bronchial Asthma," *Quart. Rev. Allergy and Applied Immun.* In press.
6 Rammelkamp, C. H.: "A Method of Determining the Concentration of Penicillin in Body Fluids and Exudates," *Proc. Soc. Exper. Biol. and Med.*, 51:95, 1942.
7 Finland, M.: "The Present Status of Antibiotics in Bacterial Infections," *Bull. New York Acad. Med.*, 27:199, 1951.
8 Bloomfield, A. L.: "Effect of Antibiotics on Bacteria of the Upper Air Passages," *Arch. Int. Med.*, 88:135, 1951.
9 Waisbren, B. A.: "Bacteremia Due to Gram-Negative Bacilli Other than the Salmonella; A Clinical and Therapeutic Study," *Arch. Int. Med.*, 88:467, 1951.
10 Wheat, R. P., Zuckerman, A. and Rantz, L.: "Infection Due to Chromobacteria," *Arch. Int. Med.*, 88:461, 1951.

The Hydriodide of Diethylaminoethyl Ester of Penicillin G, Neo-Penil

V. A Comparative Study of the Treatment of Bacterial Pneumonias with Procaine Penicillin*

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Various modifications in the chemical structure of ordinary benzyl penicillin have been made in an attempt to make it more useful. Through these attempts, hundreds of different salts of penicillin have been prepared and evaluated. But, only three of these—the sodium, potassium, and procaine salts—are widely used. In 1943 a different approach was tried in that certain esters, rather than penicillin salts, were prepared but were found to be inactive in man. Then, in 1948, in a general search for a repository form of a penicillin salt, the diethylaminoethyl ester of penicillin G was prepared, both as the hydriodide (Neo-Penil†) and the hydrochloride. When the hydriodide compound was found to have the unique property of marked diffusability into pulmonary tissues of guinea pigs,[1] it naturally suggested obvious therapeutic advantages. Further studies in cats and dogs confirmed the original observations of higher penicillin concentrations in lungs of guinea pigs, following neo-penil than after procaine penicillin.

In man, neo-penil has been shown to be a repository penicillin, but gives rise to lower and less prolonged plasma concentrations than those resulting from procaine penicillin.[2] The lower penicillin plasma concentrations following neo-penil are reflected in smaller urinary recoveries (31 per cent) as compared to 62 per cent for procaine penicillin. This smaller urinary recovery following the intramuscular administration of neo-penil can be interpreted in various ways: (1) the elimination of the antibiotic by excretory pathways other than the urinary tract; or (2) destruction of the material in the tissues of the body. According to several groups of investigators, significant quantities of penicillin are excreted in the saliva[3,4] and bronchial[5] secretions, clearly demonstrating that the drug is eliminated from the body by ways other than the kidneys. Furthermore, it is well known that penicillin is excreted in quantity in the bile, and it may be that neo-penil also is excreted in this manner. If the hydriodide of diethylaminoethyl ester of penicillin behaves as the hydrochloride, it would

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†Neo-penil is the trademark of Smith, Kline & French Laboratories, Philadelphia, for the diethylaminoethyl ester hydriodide of penicillin G. In the European literature, this ester is variously identified as Leocillin (Leo Pharmaceutical Products, Copenhagen, Denmark), as Estopen (Glaxo Laboratories, Ltd., England), as Bronchocilline (Laboratoire Roger Bellon, France), and by certain investigators as LG1, to distinguish it from the hydrochloride, which they identify as LG2.

appear likely that significant quantities of the compound are excreted in the stools. The likelihood of significant quantities of neo-penil being sequestered in the tissues of the body and being released slowly seems doubtful since the urinary excretion of penicillin approaches the limit of measurability by the end of 24 hours.

Clinical studies[4] have indicated that neo-penil is superior to other penicillin preparations in the management of certain chronic pulmonary infections, such as bronchitis and bronchiectasis. While it was reasonable to assume that it would be equally, or more, effective in the treatment of such acute pulmonary infections as bacterial pneumonias, this remained to be demonstrated by clinical trial. During the past year (1951-1952), this new penicillin compound has been studied at the Philadelphia General Hospital. The results of this controlled study, using procaine penicillin and neo-penil in the treatment of bacterial pneumonia, are reported here.

Organization of the Study

During the winter of 1951-1952, 114 pneumonia patients admitted to the adult Fever Wards of the Philadelphia General Hospital were divided into two therapeutic groups: 55 received neo-penil, and 59 received procaine penicillin. In general, the two groups were comparable as to the distribution of factors influencing prognosis. All of the patients were acutely, or at least moderately, ill and were, for the most part, indigent, poorly nourished, and chronically alcoholic. Not included in this study were several moribund patients in each group who died within 24 hours of admission. Also, there were several seriously ill patients included in both groups who received crystalline penicillin G, in addition. Hence, this controlled study is to some extent made up of a selected but comparable series of cases.

The diagnosis of pneumonia was established by the clinical history and the findings on clinical, laboratory, and x-ray examinations. Pneumococci were obtained from the sputum and/or blood stream in 62 (34 of the neo-penil treated group and 28 of the procaine penicillin treated group) patients. In cases requiring prolonged treatment, repeated cultures were made on the blood and sputum, and sensitivity studies were performed. Follow-up chest films were made in 94 of those treated.

Dosage

The dose schedule with neo-penil and procaine penicillin was 500,000 units intramuscularly daily for a total of five days of therapy. This was sufficient in 47 of the patients receiving neo-penil and 48 of those in the procaine penicillin treated group. There were five patients in each group who required therapy for 10 days because of certain complicating factors. Also, there were nine patients (three in the neo-penil treated group and six in the procaine penicillin treated group) who were given crystalline penicillin G in addition.

Results

Mortality: Of the 114 patients in this study, three died. Of these, one had received neo-penil and the other two had received procaine penicillin.

In each instance the pneumonia was complicated by some serious, pre-existing disease process. As indicated above, deaths occurring within 24 hours of admission were not included in this study.

Temperature Response to Treatment: The clinical improvement which usually accompanies the reduction of fever in pneumonia points to the probability that it represents the cessation of the invasion of toxemia-promoting elements in the infection, rather than any ordinary antipyretic process. Hence, the critical drop in temperature and its return to normal is usually considered as an index of the effectiveness of a drug in the treatment of such acute infections as bacterial pneumonia. For this study, we have considered defervescence to be complete when the oral temperature remains consistently below 99.5 degrees F. Fever curves in the early phases of therapy in the successfully treated patients showed no differences in the two therapeutic groups, as indicated in Chart I (showing the first 20 cases in each therapeutic group, which were representative of the entire group).

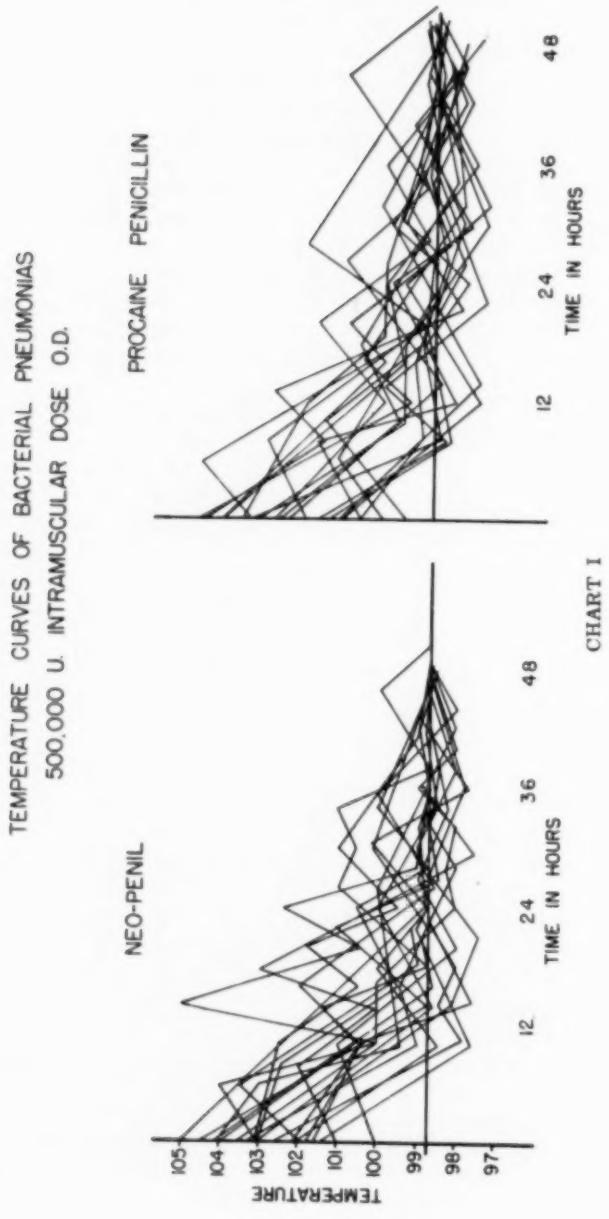
Complications: In general, the number of complications for the entire series was comparatively high. Nine patients had massive pleural effusion (four in the neo-penil treated group and five in the procaine penicillin treated group), and three developed empyema (one in the neo-penil treated group, two in the procaine penicillin treated group). There were no untoward reactions attributable to either form of penicillin therapy in this series of cases.

X-ray Evidence of Clearing: Of the 114 patients, 94 (42 in the neo-penil treated group; 52 in the procaine penicillin treated group) were followed by repeated roentgen chest studies; within two weeks approximately 75 per cent of both groups showed significant or complete resolution.

SUMMARY

A new penicillin ester, neo-penil (the diethylaminoethyl ester hydriodide of penicillin G, known generically as penethamate hydriodide), has been shown to produce higher concentrations of penicillin in certain body tissues or organs than do the commonly employed penicillin salts. The concept of penicillin derivatives having affinity for certain tissues or organs of the body is not new, but this is the first instance in which the phenomenon has been observed to a degree that is therapeutically significant. Animal and human experiments have shown that neo-penil has a far greater affinity for the lungs than have the other penicillin preparations. Since these unusually high tissue concentrations occur in the absence of high blood levels, it is felt that the tissue levels are due to the pharmacological property of the drug and not merely to a high blood-tissue diffusion gradient. Furthermore, it has been shown that neo-penil is a repository penicillin salt, but to a lesser degree than is procaine penicillin.

In an effort to obtain more information concerning the comparative effectiveness of neo-penil and procaine penicillin in bacterial pneumonia, 114 cases of the disease (55 treated with neo-penil and 59 treated with procaine penicillin) were treated with these two penicillin preparations


TEMPERATURE CURVES OF BACTERIAL PNEUMONIAS
500,000 U. INTRAMUSCULAR DOSE O.D.
PROCAINE PENICILLIN
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101
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99
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12
24
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48
TIME IN HOURS
12
24
36
48
TIME IN HOURS

CHART I

during the winter of 1951-1952. The data presented offer no significant difference between the two forms of penicillin in their ability to reduce fever. Furthermore, both forms were equally adequate as far as the end results of therapy were concerned.

RESUMEN

El Neo-penil, un nuevo ester de la penicilina (ester del yodidrato de dietilaminoetil penicilina G) ha demostrado producir mas altas concentraciones de penicilina en ciertos tejidos u órganos, que las sales de penicilina comunmente empleadas. No es nuevo el concepto de que ciertos derivados de la penicilina tengan afinidad por determinados tejidos u órganos, pero es el primer caso en que tal fenómeno se ha observado en grado que es de significación terapéptica. Los experimentos en animales y en seres humanos han mostrado que el neo-penil tiene una afinidad mucho mayor por los pulmones que cualquiera otra preparación de penicilina. Puesto que estas concentraciones elevadas se presentan sin que el tenor de la sangre sea elevado, se cree que estas concentraciones tisulares se deben a una propiedad farmacológica de la droga y no solamente a una alta difusión de la misma de la sangre hacia los tejidos. Además, se ha demostrado que el neopenil es una sal de penicilina que tiene el caracter acumulativo pero en grado menor la procaina-penicilina.

En un esfuerzo para obtener información mayor respecto de la afectividad del neo-penil y de la procaina-penicilina en la neumonia bacteriana se trataron 114 casos de la enfermedad (55 con neo-penil y 59 con procaina-penicilina) durante el invierno de 1951-1952. Los datos presentados no ofrecen diferencia significativa entre las dos formas de penicilina en su capacidad para reducir la fiebre, siendo, ambas formas igualmente adecuadas en lo que se refiere a los resultados finales del tratamiento.

RESUME

Un nouvel ester de pénicilline, le "néo-pénil," (diethylaminoethyl-ester-hydroiodide de pénicilline G, connu génériquement sous l'appellation: penethamate a'hydroiodide) s'est montré capable de réaliser une concentration de pénicilline dans certains tissus ou viscères de l'organisme plus forte que celle qu'on obtient par les sels de pénicilline habituellement employés. La conception de dérivés de pénicilline ayant une affinité particulière pour certains tissus ou certains viscères n'est pas nouvelle. Cependant, c'est la première fois que ce phénomène s'observe à un tel degré, et prend une véritable signification thérapeutique. L'expérimentation sur l'homme et sur l'animal à montré que le néopénil a une beaucoup plus grande affinité pour les poumons que toutes les autres préparations de pénicilline. Le fait que cette haute concentration dans les tissus apparait sans qu'il y ait un niveau élevé dans le sang montre que le taux tissulaire est en rapport avec les préparations pharmacologiques de la drogue, et non pas simplement avec le taux élevé de diffusion de la concentration sanguine dans les tissus. En outre, il a été démontré que le néo-pénil

constitue une réserve de pénicilline, mais à un degré inférieur à celui de la procaine-pénicilline.

Afin d'obtenir plus de renseignements sur l'effet comparatif du néopinil, et de la procaine-pénicilline, dans les pneumonies, 114 malades (55 traités par le néo-pénil, et 59 traités avec la procaine-pénicilline) ont été suivis pendant l'hiver 1951-1952. Les résultats ne montrent pas de différence marquée entre ces deux formes de pénicilline au point de vue de la réduction de la fièvre. Les deux produits ont eu une efficacité semblable.

REFERENCES

1 Jensen, K. A., Dragsted, P. J., Moller, P. and Kiaer, I.: "Investigations on Penicillin Preparations and Dosage," *Ugeskrift for Laeger*, 112:1075, 1950.
2 Flippin, H. F., Matteucci, W. V., Schimmel, N. H., Bartholomew, L. E. and Boger, W.: "The Hydriodide of Diethylaminoethyl Ester of Penicillin G, Neo-Penil. I. A Comparative Study of Plasma Concentrations and Urinary Recoveries with Procaine Penicillin," *Antibiotics and Chemotherapy*, 2:208, 1952.
3 Jensen, K. A., Dragsted, P. J., Kaier, E. J. and Fredericksen, E.: "Leocillin (Benzyl Penicillin-—-Diethylaminoethylester Hydriodide)," *Acta Path. et microbiol. Scand.*, 28:407, 1951.
4 Heathcote, A. G. S. and Nassau, E.: "Concentration of Penicillin in the Lungs, Effects of Two Penicillin Esters in Chronic Pulmnary Infections," *Lancet*, 1: 1255, 1951.
5 Flippin, H. F., Unangst, W. W., Schimmel, N. H., Bartholomew, L. E. and Matteucci, W. V.: "The Hydriodide of Diethylaminoethyl Ester of Penicillin G, Neo-Penil. II. A Comparative Study of Bronchial Secretions and Plasma Concentrations with Procaine Penicillin," *J. Phila. Gen. Hosp.*, 3:57, 1952.

The Intrabronchial Use of Streptokinase and Streptodornase in the Treatment of Slowly Resolving Pneumonia*

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Tillett and his associates[7-11] have demonstrated that the catalytic agent, Streptokinase, and the enzyme, Streptodornase, which are produced in abundance during the active growth of certain hemolytic streptococci can be effectively used for therapeutic purposes. Sherry and co-workers[5,6] found that the major constituent responsible for the viscosity of thick purulent exudates was desoxyribonucleoprotein, a substance hydrolyzed by Streptodornase. It seemed likely, therefore, that Streptokinase and Streptodornase might be used advantageously in the treatment of pulmonary suppuration with thick exudate. Healing in the parenchyma of the lung depends not only upon phagocytic action but also upon removal of exudate from the alveoli and terminal bronchioles to permit re-expansion of the involved segments. If the viscous plug in the bronchioles is completely or partially digested, the patient will cough up the retained secretion. Aeration of the alveoli served by the bronchiole and therefore expansion of the atelectatic segment will occur. The exudate in such instances is composed of fibrin, desoxyribonucleoprotein, desoxyribose nucleic acid, living and dead leukocytes and desquamated bronchial epithelium.

Tillett and Sherry,[8] studying leukocytes of purulent exudates in empyema of long standing found that masses of leukocytes were broken up when Streptodornase was introduced. Johnson[2] reported that clumping was not seen in the absence of desoxyribose nucleic acid and the clumping was probably associated with the high viscosity produced by the desoxyribose nucleic acid. The digestion of the complex nucleic acid would permit new leukocytes coming into the area to remain unclumped. Since phagocytic action is dependent upon the presence of mobile leukocytes, phagocytosis would be considerably enhanced. Johnson[2] has also reported an increase in the total number of leukocytes in a wound from influx of fresh viable cells due to the specific actions of Streptokinase and Streptodornase.

A major problem in the enzymatic treatment of infections in the parenchyma of the lung is the difficulty of establishing and maintaining contact between the enzymes and the exudate. Armstrong and White[1]

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reported favorably on the liquefaction of viscous purulent exudate by an aerosol containing desoxyribonuclease derived from ox pancreas. Muenster, Flance and Sweeney,[4] using Streptodornase, obtained liquefaction of the fibrino-purulent material in the lung of a patient who had unresolved pneumonia and achieved both a decrease of abnormal physical findings and an improvement in the roentgenographic appearance of the lung.

It is the purpose of this communication to present the case histories of two patients who had slowly resolving pneumonia and who were treated by the intrabronchial administration of Streptokinase and Streptodornase. The following method has seemed satisfactory. At the conclusion of the routine diagnostic bronchoscopy, the patient was placed so that the diseased pulmonary tissue was dependent. A catheter was passed through the bronchoscope and the enzymes injected. The bronchoscope and catheter were withdrawn and the patient requested to maintain the position for four hours if possible. Subsequent therapy was given through a catheter passed into the bronchial tree. Postural drainage with the affected area uppermost was performed four times a day. The necessary position in bed was achieved with a bed board and a Gatch bed, as described by one of us (J.M.M.).[3]

Report of Cases

Case 1: J.C.W. (R-28446), a 54 year old Negro, was admitted to the Veterans Administration Hospital, Fort Howard, Maryland, on January 31, 1951 with a complaint of pain in the vertebral column of two weeks duration. He noted a cough one week before admission and pain in the right chest and substernal region on the day before admission. Culture of the sputum showed Streptococcus pyogenes and of the blood a microaerophilic Streptococcus viridans. The initial roentgenogram of the chest revealed a homogenous infiltration of the lower two-thirds of the right lung (Figure 1).

Aqueous crystalline procaine penicillin G, 100,000 units, given intramuscularly every three hours from January 31 to February 9, had little effect. Aureomycin 0.25 gram four times a day, orally, was given from February 3 to February 9 when the dose was increased to 0.5 gram four times a day until April 4. Slight resolution

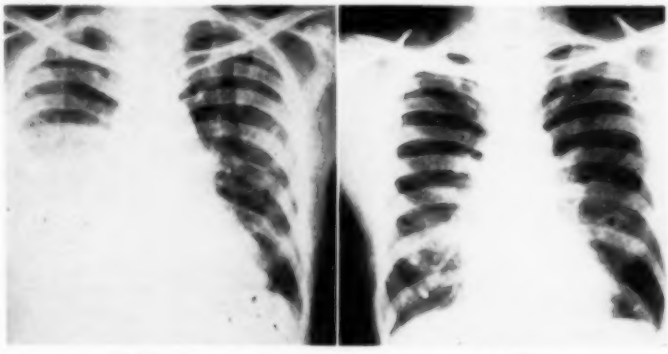

FIGURE 1 FIGURE 2

Figure 1: Roentgenogram of February 2, 1951, showing infiltration in right lung.
Figure 2: Roentgenogram of May 2, 1951, showing almost complete resolution.

of the area of infiltration was noted on the roentgenogram of February 21. Because of the suspicion that a bronchogenic carcinoma might be present, bronchoscopy was done on February 23. The mucosa of the right main bronchus was acutely inflamed but an intrinsic lesion was not found. A moderate amount of thick purulent secretion was aspirated from the orifice of the bronchus to the lower lobe of the right lung. Streptokinase, 150,000 units and Streptodornase, 50,000 units, dissolved in 10 cc. of sterile physiologic saline were put in the right main bronchus through a catheter on February 24, 26, 28 and March 2. The roentgenogram of the chest on March 2 revealed an increased area of density in the right lung, which was interpreted as a reaction to the Streptokinase and Streptodornase. Postural drainage was continued after the administration of the enzymes was stopped. The temperature, which had been elevated to 101.6 degrees F. on admission returned to normal on March 8 and remained so. Bronchoscopy on March 7 showed considerable decrease in the inflammation of the mucosa of the right main bronchus. The patient became asymptomatic. The roentgenogram of the chest showed continued resolution. He was discharged on April 4. On a return visit on May 2, he stated that he felt well. The roentgenogram of the chest showed almost complete clearing of the pneumonic process in the lower lobe of the right lung (Figure 2).

Case 2: C.A.T. (R-28529), a 70 year old white male was admitted to the Veterans Administration Hospital, Fort Howard, Maryland, on February 11, 1951 with a history of cough of three weeks duration. A lesion had been found in the right lung on the roentgenogram on February 2 by the patient's physician. Two subsequent roentgenograms did not show any improvement. The physician referred the patient for treatment of a suspected carcinoma of the right lung.

The roentgenogram of the chest taken on admission (Figure 3) showed a nonspecific irregular parenchymal infiltration involving the lower portion of the middle and inner zones of the right lung. When bronchoscopic examination was done on February 16, a large amount of secretion was seen to come from the orifice of the bronchus of the lower lobe of the right lung. The pus contained pneumococci in pure culture. Examination of bronchial washings showed normal bronchial epithelium. Streptokinase 100,000 units and Streptodornase 60,000 units dissolved in 10 cc. of sterile physiologic saline were administered through a catheter into the bronchus under direct vision. Streptokinase 150,000 units and Streptodornase

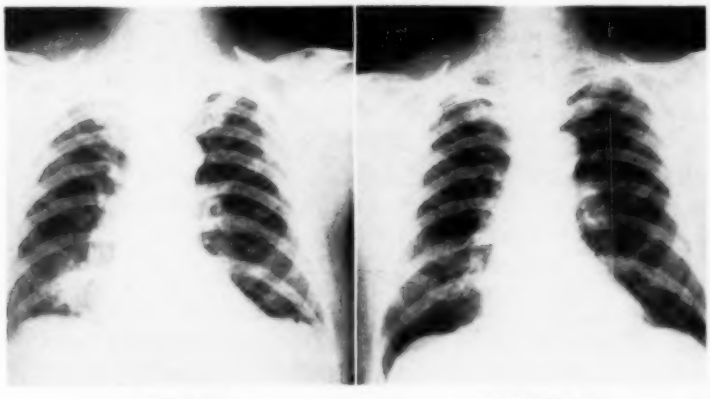

FIGURE 3 FIGURE 4

Figure 3: Roentgenogram of February 12, 1951, showing infiltration in right lung.
Figure 4: Roentgenogram of April 30, 1951, showing almost complete resolution.

50,000 units dissolved in 10 cc. of physiologic stline were given by intratracheal catheter on February 18, 20, 22, 24, 26, 28 and March 2. Following each treatment, the patient was placed with the lower lobe of the right lung lowermost and asked to keep that position for four hours. This was readily accomplished using the tilted bed. During the period of enzyme therapy, he produced much larger quantities of sputum and examination of the sputum did not show malignant cells. Other chemotherapeutic or antibiotic agents were not given. A comparison of the roentgenogram of February 20 with those of February 26 and March 2 shows an increase in the size of the opacity probably caused by Streptokinase and Streptodornase. The roentgenogram of the chest taken on April 2 showed marked clearing. He was discharged from the hospital on April 4. On a return visit on April 30, the roentgenogram of the chest (Figure 4) showed almost complete resolution.

Comment

Bronchoscopic examination should always precede the use of Streptokinase and Streptodornase, because a bronchogenic carcinoma, which could cause the pulmonary infiltration and atelectasis, might be detected. Furthermore, the mechanical removal of purulent exudate by aspiration at the time of bronchoscopy is a definite, although at times temporary, help in the treatment of atelectasis.

The intrabronchial instillation of Streptokinase and Streptodornase is contraindicated in the presence of active pulmonary tuberculosis to avoid possible bronchogenic spread of the disease. All examinations possible to eliminate the presence of tuberculosis should be done before treatment is started.

The use of these agents in the presence of undiagnosed carcinoma with negative bronchoscopy might be an advantage in diagnosis. The loosening of plugs of cellular debris from terminal bronchioles and the influx of serum provide large quantities of sputum for direct examination for tumor cells. This material is similar to that obtained by bronchial washing at the time of bronchoscopy. Repeated examinations of bronchial exudate may thus be made without additional bronchoscopy.

SUMMARY

Streptokinase and Streptodornase may be useful adjuncts in the treatment of slowly resolving pneumonia. Two patients have been so treated with excellent results.

RESUMEN

La estreptokinasa y la estreptodornasa pueden ser auxiliares útiles en el tratamiento de la neumonía de resolución lenta. Dos enfermos fueron tratados así con excelentes resultados.

RESUME

La streptokinase et la streptodornase peuvent être des auxiliaires précieux dans le traitement des pneumopathies lentement résolutives. Deux malades ont été traités par ce moyen avec des résultats excellents.

REFERENCES

1 Armstrong, J. B. and White, J. C.: "Liquefaction of Viscous Purulent Exudates by Desoxyribonuclease," *Lancet*, 2:739, 1950.

2 Johnson, A. J.: "Cytological Studies in Association with Local Injections of Streptokinase-Streptodornase in Patients," *J. Clin. Investigation*, 29:1376, 1950.
3 Miller, J. M.: "Substitute for Shock Blocks," *Am. J. Nursing*, 52:205, 1952.
4 Muenster, J. J., Flance, I. J. and Sweeney, B.: "The Treatment of Unresolved Pneumonia with Streptokinase and Streptodornase," Referred to in Varidase, Streptokinase-Streptodornase, an effective physiologic curette, Lederle Laboratories, Inc., New York City, New York, 1951.
5 Sherry, S. and Goeller, J. P.: "The Extent of the Enzymatic Degradation of Desoxyribonucleic Acid (DNA) in Purulent Exudates by Streptodornase," *J. Clin. Investigation*, 29:1588, 1950.
6 Sherry, S., Tillett, W. S. and Christensen, L. R.: "Presence and Significance of Desoxyribose Nucleoprotein in the Purulent Pleural Exudates of Patients," *Proc. Soc. Exper. Biol. and Med.*, 68:179, 1949.
7 Sherry, S., Tillett, W. S. and Read, C. T.: "The Use of Streptokinase-Streptodornase in the Treatment of Hemothorax," *J. Thoracic Surg.*, 20:393, 1950.
8 Tillett, W. S. and Sherry, S.: "The Effect in Patients of Streptococcal Fibrinolysin (Streptokinase and Streptococcal Desoxyribonuclease) on Fibrinous, Purulent and Sanguineous Pleural Exudations," *J. Clin. Investigation*, 28:173, 1949.
9 Tillett, W. S., Sherry, S., Christensen, L. R., Johnson, A. J. and Hazelhurst, G.: "Streptococcal Enzymatic Debridement," *Ann. Surg.*, 131:12, 1950.
10 Tillett, W. S., Sherry, S. and Road, C. T.: "The Use of Streptokinase-Streptodornase in the Treatment of Post-pneumonic Empyema," *J. Thoracic Surg.*, 21: 275, 1951.
11 Tillett, W. S., Sherry, S. and Read, C. T.: "The Use of Streptokinase-Streptodornase in the Treatment of Chronic Empyema. With an Interpretive Discussion of Enzymatic Actions in the Field of Intrathoracic Diseases," *J. Thoracic Surg.*, 21:325, 1951.

Serum Mucoproteins in Pulmonary Tuberculosis*

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In view of the fact that there is a need for a simple and objective laboratory procedure to aid in the determination of prognosis, extent and state of activity of pulmonary tuberculosis, it appeared justified to report experiences with mucoproteins and polysaccharides. This need has become more urgent with the discovery of new chemotherapeutic and antibiotic agents, as well as the development of definitive surgical procedures for the treatment of the disease. Many tests have been suggested for the laboratory evaluation of the status of the patient but few have been widely accepted. All the tests show a wide range of results in normal and abnormal conditions as well as unexplained discrepancies. These tests include various hematologic determinations, such as: the Arneth index,[1] the differential leukocyte count,[2] the monocyte count,[3] and the lymphocyte-monocyte ratio,[4] as well as serum protein studies, particularly the A/G ratio,[5] and the gamma globulins.[6] Only two procedures, bacteriologic studies and the sedimentation rate, remain in general usage. The sedimentation rate is of value in establishing the presence or absence of activity but it is influenced by a multitude of extraneous factors. Its greatest value lies in serial determinations in the individual patient if all factors such as abnormal hematocrit are taken into account and the presence of other diseases are ruled out. Bacteriologic studies, unfortunately, do not necessarily mirror the extent or amount of activity in the disease process. Furthermore, these procedures give little evidence as to the patient's resistance. In the search for a tool to measure these factors various serum proteins were investigated.

Carbohydrate-rich proteins have long been known to exist in human serum.[7] Their nature and chemical properties were largely clarified by the observations of Winzler, et al. who termed them serum mucoproteins.[8] Their studies were based upon determination of the protein fraction in a serum precipitate. Attempts have been made to use elevation of these mucoproteins in the detection of cancer.[9,10] However, elevated values were also found in liver disease,[11,12] myocardial infarction,[13] and pneumonia.[9] Increase in total serum polysaccharides have been found in various chronic diseases such as: carcinoma, tuberculosis, sarcoidosis, hyperthyroidism and cardiovascular disease.[6,14] At least a part of these polysaccharides are carbohydrate moieties bound to protein, particularly the mucoproteins, and therefore their elevation is probably an expression of increased serum mucoprotein. A recent attempt was made to specifically determine the carbohydrate moiety in the isolated protein precipitate.[15,16]

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This report is confined to the significance of protein and carbohydrate moieties in the mucoproteins and the ratio between them in the elevation and prognosis of pulmonary tuberculosis. The behavior of these substances in serial studies in individual cases will be reported later.

Material and Methods

After careful clinical evaluation, including x-ray and laboratory studies, blood was drawn from 109 patients with pulmonary tuberculosis and 18 normal controls (hospital personnel). The patients were divided according to the classification of the National Tuberculosis Association.[18] Of the 109 patients, 18 were arrested cases (two minimal, six moderately advanced, and 10 far advanced). Active pulmonary tuberculosis was found in 91 cases (18 minimal, 18 moderately advanced, and 55 far advanced).

The protein moiety of the serum mucoproteins was determined according to the method of Winzler, et al. using phosphotungstic acid precipitation followed by determination of the tyrosine (phenol) content in the precipitate.[7] Results are expressed in mg. per 100 ml. of serum. The polysaccharide moiety in the protein precipitate was determined by the modification of Ayala et al.[15] of the method of Niazi and State,[16] employing the purple color reaction which develops after heating the trichloracetic acid precipitate with diphenylamine reagent. Results are expressed directly in the optical density reading obtained on a Leitz-Rouy photrometer, making the readings at 535 mu.

Means, standard deviations, and percentage distributions of results were calculated for mucoproteins, polysaccharides, and the polysaccharide-mucoprotein ratio (multipled by 10). After a period of six months observation, the clinical status of the patients with far advanced tuberculosis was evaluated and compared with the original laboratory findings.

Results:

There was only a slight increase above the normal serum mucoprotein level in all the groups examined except in the group with far advanced pulmonary tuberculosis (Table I). The mean value of this level is statis-

TABLE I: Means and Standard Deviations of Serum Mucoproteins, Polysaccharides and the Polysaccharide/mucoprotein Ratio (X 10) in Various Stages of Pulmonary Tuberculosis.

	Number of Cases	Mucoproteins (mg. per 100 ml.)		Polysaccharides		P/M Ratio (X 10)	
Normal	18	1.98	0.63	0.217	0.054	1.20	0.61
Arrested	18	2.28	0.51	0.218	0.050	1.06	0.42
Active:							
Minimal	18	2.28	0.76	0.178	0.035	0.87	0.40
Moderate	18	2.41	1.17	0.199	0.053	0.95	0.26
Far Advanced	55	5.04	1.99	0.303	0.144	0.73	0.29

tically higher (T value above 3.00) in the group with far advanced disease than in any of the other group. The mucoprotein values were above 4.0 mg. per 100 ml. in 64 per cent of the far advanced cases while a similarly high value was found in only one other patient (in the moderately advanced group) (Table II). The highest value observed was 11.73 mg. per 100 ml.

In the polysaccharide fraction, lower than normal mean values were found in the minimal and moderate groups while in the group with far advanced disease the mean was elevated (Table I). Over 50 per cent of the latter group had values above 0.30 while this was seen in only two other cases, one arrested and one moderately advanced (Table III). The polysaccharide-mucoprotein ratio (times 10) showed a drop in the active forms of the disease. This drop was more marked in the far advanced group (Table I). In general, the drop was due to a disproportionate increase in the mucoprotein level. Study of the percentage distribution of the ratios showed a marked overlapping (Table IV).

Of the patients with far advanced pulmonary tuberculosis, 41 were followed for six months after the initial laboratory studies. Of these 13 had improved, 22 had either remained stationary or had deterioriated, and six had died. All six who expired had mucoprotein levels above 6.0 mg. per 100 ml. The two patients with levels above 10.0 mg. per 100 ml. were also in this group. In the surviving patients, no significant difference of the mucoproteins were found between those who improved and those who did

TABLE II: Percentage Distribution of Serum Mucoprotein Levels in Various Stages of Pulmonary Tuberculosis.

	0-2.0 mg. per 100 ml.	2.0-4.0 mg. per 100 ml.	4.0-6.0 mg. per 100 ml.	6.0 Plus mg. per 100 ml.
Normal	61	39		
Arrested	50	50		
Active:				
Minimal	33	67		
Moderate	44	50	6	
Far Advanced	4	31	33	31

TABLE III: Percentage Distribution of Serum Polysaccharides Expressed in Optical Density Readings in Various Stages of Pulmonary Tuberculosis.

	0-0.20	0.20-0.30	0.30-0.40	0.40 Plus
Normal	39	61		
Arrested	44	50	6	
Active:				
Minimal	72	18		
Moderate	44	50	6	
Far Advanced	20	26	42	11

not (Table V). The polysaccharide value showed no significant difference in the patients who improved, those who did not improve and those who died. However, the ratio was below one in 38 per cent of the improved cases while it was below one in 86 and 100 per cent respectively in the groups who failed to improve or died.

Discussion

The elevation of the serum mucoproteins and polysaccharides in neoplastic,[9,10] as well as inflammatory[6,9,14] diseases suggest their origin from the reticuloendothelial system. Abnormal elevation of these substances may therefore mirror stimulation of this system, but it was also suggested that it may be indicative of tissue breakdown[13] or might be related to hepatic function, particularly protein formation.[11-13] Any one of these three possibilities may account for the changes seen in pulmonary tuberculosis although the lack of correlation with gamma globulin levels[6] speaks against the possibility of reticuloendothelial stimulation. The independent behavior of each of the mucoprotein and polysaccharide fractions found in this study also suggests that they may have different origins.

Despite the fact that the relation of these fractions to one another as well as their origin are not fully understood, the determinations of mucoproteins and polysaccharides are expected to be of possible value in patients with pulmonary tuberculosis. The results obtained indicate that high mucoprotein levels in the presence of known pulmonary tuberculosis

TABLE IV: Percentage Distribution of Serum Polysaccharide mucoprotein Ratio (X 10) in Various Stages of Pulmonary Tuberculosis.

	Less than 0.50	0.50-1.00	1.00-1.50	More than 1.50
Normal		39	22	39
Arrested	6	50	38	6
Active:				
Minimal	16	67	11	6
Moderate	6	50	44	
Far Advanced	24	52	24	

TABLE V: Clinical Status of 41 Patients with Far Advanced Pulmonary Tuberculosis After Six Months Compared with the Results of Initial Mucoprotein and Polysaccharide Determinations.

Status of Patients Six Months After Initial Test	Number of Patients	Percentage with Mucoprotein Above 4 mg. per 100 ml.	Percentage with Polysaccharide Above 0.30	Percentage with Polysaccharide/ Mucoprotein Ratio Below 1.0
Improved	13	46	54	38
Unimproved	22	55	32	86
Expired	6	100	50	100

strongly suggest that the disease is far advanced. Furthermore, when this is associated with a lowered polysaccharide-mucoprotein ratio the chances that the patient will respond well to therapy is reduced. Extremely high mucoprotein levels seems to indicate the probability of fatal outcome of the disease. In less severe cases, individual determinations are of little value since the results do not differ materially from the normal. Serial determinations in these cases will provide evidence of progression in the form of an increase in mucoproteins with a decrease in the polysaccharide-mucoprotein ratio. The reverse is also true, that regression of far advanced pulmonary tuberculosis will be characterized by a decrease in the mucoproteins and an increase in the ratio.

It appears that determination of the protein fraction of the mucoprotein according to the method of Winzler et al.[5] is promising in the management of the patient with pulmonary tuberculosis. It should encourage studies on a larger number of patients and serial studies in the same patient. The use of the diphenylamine reaction in the protein precipitate, as such, offers little promise. However, additional studies will be necessary to determine whether the mucoprotein-polysaccharide ratio is sufficiently informative to warrant further study.

Acknowledgements: Thanks are due to Dr. Hans Popper for originating and supervising this study, and to Miss Janice Christensen for technical assistance.

SUMMARY

The serum mucoproteins (determined as their protein moiety), polysaccharides in serum proteins (determined by the diphenylamine reaction) and a ratio between them were determined in 109 patients with pulmonary tuberculosis in various stages and in 18 normal controls. The mucoproteins were significantly elevated in far advanced stages of the disease. Extremely high values are apparently associated with a fatal outcome. The variations of the polysaccharides are not diagnostic. The polysaccharide-mucoprotein ratio is reduced in far advanced tuberculosis. However, further studies are required to establish whether this decrease means more than the elevation of the mucoproteins.

RESUMEN

Las mucoproteínas del suero, los polisacáridos en las proteínas del suero (determinados por la reacción de la difenilamina) y una relación entre ellas, fueron determinados en 109 enfermos de tuberculosis en varios etapas y en 18 controles normales.

Las mucoproteínas se encontraron significativamente elevadas en las etapas muy avanzadas de la enfermedad. Los valores más altos de ellas se encontraron aparentemente asociados a una evolución fatal. Las variaciones de los polisacáridos no son de valor diagnóstico. La relación polisacáridosmucoproteínas es reducida en la tuberculosis muy avanzada. Sin embargo se requieren estudios ulteriores para establecer si esta disminución significa más que la sola elevación de las mucoproteínas.

RESUME

Les mucoprotéines du sérum et les polysaccharides des protéines sériques furent calculées chez cent-neuf malades atteints de tuberculose pulmonaire à des degrés divers et chez dix-huit individus normaux choisis comme témoins. Les mucoprotéines étaient nettement élevées dans la période très avancée de la maladie, les quantités extrêmement élevées se trouvent apparemment dans les cas d'évolution mortelle.

Dans la tuberculose avancée, le taux des polysaccharides est réduit. Des études ultérieures sont nécessaires pour savoir si cette chute des polysaccharides a plus de signification que l'augmentation du taux des mucoprotéines.

REFERENCES

1 Arneth, J.: "Die Lungenschwindsucht auf Grundlage klinischer und experimenteller hamatologischer Untersuchungen," *Ztschr. f. Tuberkulose*, 7:309, 1905.
2 Medlar, E. M. and Kastlin, G. J.: "The Polymorphonuclear Leukocyte in the Tuberculous Blood Picture," *Am. J. Med. Science*, 173:824, 1927.
3 Cunningham, R. S., Sabin, F. R., Sugiyama, S. and Kindwall, J. A.: "The Role of the Monocyte in Tuberculosis," *Bull. Johns Hopkins Hospital*, 37:231, 1925.
4 Morriss, W. H. and Tan, S. H.: "The Differential Leucocyte Count in Pulmonary Tuberculosis. The Value of the Lymphocyte-Monocyte Ratio in the Determination of Activity," *Am. Rev. Tuberc.*, 16:729, 1926.
5 Sweany, H. C., Weathers, A. T. and McCloskey, K. L.: "The Chemistry of the Blood in Tuberculosis," *Am. Rev. Tuberc.*, 8:405, 1924.
6 Seibert, F. B., Seibert, M. V., Atno, A. J. and Campbell, H. W.: "Variation in Protein and Polysaccharide Content of Sera in the Chronic Diseases, Tuberculosis, Sarcoidosis and Carcinoma," *J. Clin. Investigation*, 26:90, 1947.
7 Bywaters, H. W.: "Uber Seromucoid," *Biochem. Ztschr.*, 15:322, 1909.
8 Winzler, R. H., Devor, A. W., Mehl, J. W. and Smyth, I. M.: "Studies on the Mucoproteins of Human Plasma. I. Determination and Isolation," *J. Clin. Investigation*, 27:609, 1948.
9 Winzler, R. J. and Smyth, I. M.: "Studies on the Mucoproteins of Human Plasma. II. Plasma Mucoprotein Levels in Cancer Patients," *J. Clin. Investigation*, 27:617, 1948.
10 Greenspan, E. M., Lehman, I., Graff, M. M. and Schoenbach, E. B.: "A Comparative Study of Serum Glycoproteins in Patients with Parenchymatous Hepatic Diseases or Metastatic Neoplasia," *Cancer*, 4:972, 1951.
11 Waldstein, S. S., de la Huerga, J. and Popper, H.: In preparation.
12 Greenspan, E. M., Tepper, B., Terry, L. L. and Schoenbach, E. B.: "The Serum Mucoproteins as an Aid in the Differentiation of Neoplastic from Primary Parenchymatous Liver Disease," *J. Lab. and Clin. Med.*, 39:44, 1952.
13 Simkin, B., Ergman, H. C. and Prinzmetal, M.: "Studies on Coronary Circulation. V. Quantitative Changes in a Serum Mucoprotein Following the Occurrence of Myocardial Infarction," *Am. J. Med.*, 6:734, 1949.
14 Israel, H. L., Webster, M. B. and Maher, I. E.: "Clinical Value of Serum Polysaccharides by the Tryptophane-perchloric Acid Reaction," *Am. J. Med.*, 6:745, 1949.
15 Ayala, W., Moore, L. V. and Hess, E. L.: "The Purple Color Reaction Given by Diphenylamine Reagent. I. With Normal and Rheumatic Fever Sera," *J. Clin. Investigation*, 30:781, 1951.
16 Niazi, S. and State, D.: "The Diphenylamine Reaction of Human Serum," *Cancer Research*, 8:653, 1948.
17 Shedlovsky, T. and Scudder, J. A.: "A Comparison of Erythrocyte Sedimentation Rates and Electrophoretic Patterns of Normal and Pathologic Human Blood," *J. Exper. Med.*, 75:119, 1942.
18 National Tuberculosis Association: "Diagnostic Standards and Classification of Tuberculosis," 1951 Edition, New York.

Segmental Resection for Pulmonary Tuberculosis*

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The value of segmental resection in the therapy of pulmonary tuberculosis continues to be a matter for discussion. The work of Churchill,[1] Blades,[2] Overholt,[3] and others has demonstrated that it is possible, anatomically, to excise any segment of either lung. Several important questions remain to be solved, however: 1) Are the results following segmental resection satisfactory in comparison with those obtained by older methods of collapse therapy? 2) Is the procedure safe? 3) Are the complications following it prohibitive? An attempt will be made in this paper to answer the second and third questions. Data will be considered which may be of value in obtaining the final answer to the first.

Chamberlain[4] has emphasized the fact that much of the prejudice against segmental resection stems from a reluctance to cut across tissue with gross or microscopic tuberculous involvement. He has shown, however, that in the majority of lobectomies for tuberculosis, diseased areas are transected. It is only in the unusual case that a complete separation of the fissures between the upper and lower or the upper and middle lobes exists. Freedom from postoperative complications, therefore, often depends upon a correct evaluation of the activity of the lesion remaining in situ in the pulmonary parenchyma after resection.

We have recently reviewed a series of 50 consecutive segmental resections performed upon 46 patients between February 7, 1947, and January 8, 1952. Thirty-two patients were white; 14 were Negro. Tuberculosis had been present for an average period of 3.5 years prior to surgery. The duration of disease prior to surgery in the group who developed complications was 2.8 years and in those who did not develop complications the duration was 4.2 years. The right side was involved in 24 resections and the left in 26.

A total of 54 segments and 20 subsegments were removed. In addition to the segmental and subsegmental resections, lobectomy was done in three patients and decortication in six. The apical and posterior segments individually or in combination were removed from 35. The superior segment of the lower lobe was involved in nine, the anterior segment in 11, the lingula in two, and the basal segments of the lower lobe in five. The postoperative follow-up period ranged from one to 52 months with an average of 10.6 months. Twenty-two patients have been followed from one to six months; 20 from seven to 12 months; and eight from 13 to 52 months. The indication for operation has been the presence of a localized lesion in 42 resections and a residual postthoracoplasty cavity in eight resections.

Chamberlain has emphasized the necessity of measuring the patient's

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resistance prior to surgery by means of careful clinical, laboratory, and x-ray examinations. In this study an attempt has been made to correlate the stability of the lesion, as determined by a review of the entire series of x-ray films, and the activity of the pathological process in the excised segment with the final results. Each series of x-ray films was reviewed individually by three physicians and the final determination of the character of the lesion made by consensus of these three opinions. Lesions were classified as stable, retrogressive or progressive.

The same type of review was made upon the pathological reports of the excised specimens. Here the lesion was classified as relatively inactive or active, depending upon the amount and character of fibrosis, the degree of lymphocytic infiltration, with or without lymphoid follicles, adjacent to the lesion, the presence of bronchial ulceration, and evidence of tuberculous pneumonitis. In our series, 25 pathologically inactive and 25 active lesions were removed. Cavitary lesions were present in 30 patients and caseous nodules or inspissated cavities in 18. Tuberculous bronchiectasis was found in two.

When the lesions were classified by x-ray characteristics, it was found that 19 patients were considered stable by x-ray, 19 were retrogressive and 12 were considered progressive.

Comparison of the x-ray and pathological classifications of the 50 patients showed no parallelism between the retrogressive, stable and progressive x-ray characteristics and the pathological activity of the lesions. An individual study revealed that there was a gross incompatibility in 10 of the 50 patients. The incompatibility was found in the fact that two of our patients who were considered to have progressive x-ray lesions were classified as inactive when the pathological report was studied. In a similar manner, eight patients whose lesions were considered to be stable on examination of the serial x-ray films were found to have pathologically active lesions. Comparison of the x-ray and pathological characteristics of the lesions is shown in Table I.

The technique employed followed closely that described by other earlier workers in that the segmental bronchus was usually isolated and divided

TABLE I

COMPARISON OF X-RAY CHARACTERISTICS OF LESIONS ACCORDING TO PATHOLOGICAL ACTIVITY

X-ray Appearance of Pathologically Active Lesions:	
Stable	8
Retrogressive	7
Progressive	10
X-ray Appearance of Pathologically Inactive Lesions:	
Stable	11
Retrogressive	12
Progressive	2

first. Slight tension was then placed upon the bronchus and the arteries ligated and divided. An attempt was made to preserve the intersegmental veins whenever possible. In place of the wedge resection for a localized, small focus, we have usually palpated the bronchus leading to the involved area between the thumb and the index finger and have been able to dissect out the bronchus and do an individual ligation technique upon a subsegment. In this manner the caseous nodule involved with a small amount of surrounding parenchyma was resected. We have not covered the raw surface with a pleural flap as described by Chamberlain and Sampson.[5] We agree that early reexpansion is vital to the success of the procedure and employ suction drainage for at least 72 hours following resection.

The success of resection for tuberculosis can be measured in terms of the number of bronchopleural fistulae that develop postoperatively. It is the single complication that determines the success or failure of the procedure. Postoperative spread can be reduced to minimal levels by careful preoperative preparation and skillful management of the anesthesia. Empyema in the absence of a fistula is not a serious problem.

Bronchopleural fistula was encountered following 13 resections, or 26 per cent of the series. In comparison with other reports, this is a high percentage of postoperative fistulae. Four of them were of temporary nature, however, and probably represented air leaks from the denuded areas rather than a breakdown of the bronchial closure. The temporary fistulae were treated successfully by closed suction drainage and limited thoracoplasty done from one week to 6.5 months after the original operation. Nine of the fistulae, or 18 per cent of the series, were persistent and significant. In one patient two operative procedures consisting of fistulectomy were required to close the fistula. In two patients the fistulae were successfully treated by further pulmonary resection. The fistula in one patient was closed by thoracoplasty. In another the fistula healed after a portion of the thoracotomy wound was reopened. Fistulae in four patients have been present for 12.5, 11.5, 2.0 and 2.0 months following the segmental resections, although revision thoracoplasty was done in the first patient, and postresection thoracoplasty in the second. These fistulae were diagnosed on an average of 39 days postoperatively. Of the eight patients who had resection following thoracoplasty, only one, or 12.5 per cent, developed fistula. In this patient the fistula has been present for 13 months. Eleven of the 31 with cavitary lesions, or 35.5 per cent of this group, developed fistulae. Of the 17 with nodular disease or inspissated cavities, only two developed fistulae. This represented 11.7 per cent of that group. A primary subsegmental resection was done in 11 patients. One of these developed a temporary fistula, and in three others the fistulae were persistent. One postoperative spread occurred. A fistula rate of 36.4 per cent, or a complication rate of 45.5 per cent was found in this primary subsegmental group. Two of the six who had a decortication of the remaining lung at the time of segmental resection developed temporary fistulae. These were treated by thoracoplasty. Postoperative spread developed in one patient.

In the attempt to correlate the development of fistulae with the x-ray

and pathological classification, the following situation was encountered. Fistulae followed 16.6 per cent of operations in patients who were considered to have a stable lesion by x-ray, 26.3 per cent in those with a retrogressive lesion and in 33.3 per cent of those with a progressive lesion. From a pathological aspect, 16 per cent of the patients whose lesions were classified as inactive developed a fistula, as compared to 36 per cent of those with active lesions.

We are confident, from clinical observation, that the patient upon whom a segmental resection is contemplated should have a stable x-ray lesion and a predominance of fibrosis in the involved pulmonary area. Exceptional cases are needed to prove every rule. Five of our patients illustrated this point. All had x-ray evidence of limited perifocal spread or increase in size of the diseased area shortly before operation and were classified as active when the excised specimen was examined. All had exemplary postoperative courses and have continued without complication for over 5.5 months.

Early postoperative spread was encountered in two patients, one of these being associated with fistula. There was a late progression of disease in five. This appeared four months to one year following the original operation. There has been no death, either early or late.

In other studies[6-8] we have found that previous treatment with streptomycin results in an increased number of postoperative complications. We were interested to find that the same phenomenon was encountered in this group of segmental resections. Nineteen patients had received one or more courses of streptomycin prior to their resection course. Eight, or 42.1 per cent, developed a fistula. Thirty-one had not been given streptomycin before their resection course. Only five, or 16.7 per cent, of these developed fistulae, four of which proved to be temporary. Six of these 31 patients received long-term continuous courses of streptomycin ranging from 77 to 248 days prior to segmental resection. None of these developed a fistula.

TABLE II
RESULTS IN SEGMENTAL RESECTION

Number of Patients	Number of Resections	Significant Fistulae		Temporary Fistulae	
		No.	Pct.	No.	Pct.
46	50	9	18	4	8

Early Spread		Late Progression		Deaths		Satisfactory	Unsatisfactory
No.	Pec.	No.	Pct.	Early	Late	Number	Number
2	4	5	10	0	0	36	10

The results and complications are illustrated in Table II. Satisfactory results were ultimately obtained in 36 patients, or 78 per cent of the patients in this series. They now have negative sputum. The sputum of 25 has been consistently negative for acid-fast organisms since operation. Four in this group had positive sputa on isolated examinations during the

early postoperative days. No clinical or x-ray evidence of active disease was present, however. Seven had positive sputum associated with a fistula, spread or bronchiectasis. All of these obtained a negative sputum when the underlying cause was removed.

Unsatisfactory results were obtained in 10 patients, or 22 per cent of the series. These still have clinical or x-ray evidence of active disease or a bronchopleural fistula. Some of these 10 patients are expected to have a satisfactory result after other surgical measures are completed.

SUMMARY

1) Satisfactory end results and an acceptable complication rate can be obtained with segmental resection.

2) The ideal lesion for this type of operation is a localized, inspissated nodule which has been stable or slowly retrogressive for four to six months.

3) Resection of subsegments and the use of concomitant decortication results in an increase in the rate of complications.

4) The best results were obtained in patients who had prior thoracoplasty.

5) A higher rate of complications was encountered in patients who had been treated with interrupted courses of streptomycin prior to operation. Long-term continuous preoperative treatment with streptomycin and para-aminosalicylic acid seemed to result in a minimum of postoperative complications.

RESUMEN

1) Con la resección segmentaria se pueden obtener resultados satisfactorio finales y una aceptable proporción en los complicaciones.

2) La lesión ideal para este tipo de operación es el nódulo localizado, empastado que ha permanecido estable o en lenta regresión por cuatro a seis meses.

3) La resección de subsegmentos y el uso de la decorticación concomitante acarrean un aumento en la proporción de complicaciones.

4) Los mejores resultados se obtienen en los enfermos que han tenido antes toracoplastia.

5) Un proporción mayor de complicaciones se ha observado en aquellos enfermos que se han tratado con series interrumpidas de estreptomicina antes de la operación. El tratamiento prolongado antes de la operación con estreptomicina y ácido paraminosalicílico pareció producir con un complicaciones mínimas.

RESUME

1) On peut obtenir grâce à la résection segmentaire des résultats satisfaisants, et une proportion non excessive de complications.

2) La lésion idéale pour ce type d'opération est le nodule localisé, d'apparence fibreuse, qui est resté stable ou qui n'a que peu rétrocéde pendant quatre à six mois.

3) Lorsqu'on pratique la résection de sous-segments et qu'on utilise une décortication associée, on obtient une augmentation du taux des complications.

4) Les meilleurs résultats ont été obtenus chez les malades qui avaient eu antérieurement déjà une thoracoplastie.

5) Les malades qui avaient été traités avant l'intervention par des séries interrompues de streptomycine, donnèrent une proportion plus élevée de complications. Un traitement préopératoire de longue durée par la streptomycine associée au P.A.S. semble réduire de façon notable les complications post-opératoires.

REFERENCES

1 Churchill, E. D. and Belsey, R.: "Segmental Pneumonectomy in Bronchiectasis," *Ann. Surg.*, 109:481, 1939.
2 Blades, B.: "Conservation of Lung Tissue by Partial Lobectomy," *Ann. Surg.*, 118: 353, 1943.
3 Overholt, R. H. and Langer, L.: "New Technique for Pulmonary Segmental Resection. Its Application in Treatment of Bronchiectasis," *Surg. Gynec. and Obst.*, 84:257, 1947.
4 Chamberlain, J. Maxwell and Klopstock, Robert: "Further Experiences with Segmental Resection in Tuberculosis," *J. Thoracic Surg.*, 20:843, 1950.
5 Samson, P. C.: Discussion of Paper by Chamberlain, J. M. and Ryan, C. H.: "Segmental Resection in Pulmonary Diseases," *J. Thoracic Surg.*, 19:220, 1950.
6 Murphy, J. D., Seiler, H. H. and Walkup, H. E.: "Complications Following Pulmonary Resection for Tuberculosis in Streptomycin Treated Patients," *Minutes of Eighth Streptomycin Conference*, pp. 182-185, 1949.
7 Murphy, James D., Walkup, Harry E., Seiler, Hawley H. and Bornstein, S.: "Complications Following Pulmonary Resection for Tuberculosis in Streptomycin Treated Patients," *Dis. of Chest*, 19:493, 1951.
8 Murphy, James D. and Swindell, H. H.: "The Influence of Streptomycin Resistance Upon the Success of Cavernostomy for Thoracoplasty Failure," *J. Thoracic Surg.*, 22:104, 1951.

Patent Ductus Arteriosus with Endarteritis*

Report of a Case Complicated by Pulmonary Infarction, Treated by Ligation of the Ductus and Segmental Pulmonary Resection.

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Surgical interruption of a persisting ductus arteriosus is now a standard and safe procedure. Many series of cases treated surgically have been reported from different parts of the world. The operative mortality is low, whereas it is well established, from the observations of Bullock et al.[1] and others[2] that the mortality and morbidity in untreated cases is comparatively high.

Graybiel, Strieder and Boyer[3] in 1938, first attempted ligation of a patent ductus arteriosus in a patient with subacute bacterial endarteritis. In their case the ductus was not completely obliterated and the patient died on the fourth postoperative day. Two years later Gross and Hubbard[4] carried out a successful ligation in an uncomplicated case and shortly thereafter Touroff and Vessell[5] divided a ductus in a patient with subacute bacterial endarteritis following which the patient made a complete recovery. Such successful treatment has become more common with the advent of penicillin and other antibiotics. Usually the infection factor can be brought under control, temporarily at least, by chemotherapeutic measures. In cases where vegetations have not become established on the endocardium, closure of the ductus aids in sterilizing the bloodstream and published results indicate that only rarely has subacute bacterial infection become manifest again.

Conklin[6] published 12 cases treated surgically, one of which had subacute bacterial endarteritis and he quotes Shapiro[7] who collected 626 cases from the literature in which the ductus had been treated surgically by 43 surgeons. In this group of 626, 88 had had subacute bacterial endarteritis. The mortality in the infected group was 28.4 per cent compared with a rate of slightly over 3 per cent for the uncomplicated group.

In the cases reported here, in addition to closure of the ductus, which was complicated by probable subacute bacterial endarteritis, a segment of infarcted lung was resected and the patient discharged as cured.

Mr. K. G., C.M.C.H. 106,465: This 40 year old farmer was admitted to the hospital on December 15, 1950, with a chief complaint of chills and fever of three months' duration. At the time of his first attack three months previously he consulted a physician and was hospitalized. A diagnosis of patent ductus arteriosus was made and surgical treatment advised. The patient, however, elected to have surgery deferred. Under medical treatment, the chills and fever disappeared and he was discharged asymptomatic. Shortly thereafter an irregular fever again appeared and had been present up to the time of admission. No history of any embolic phenomena could be elicited. For the past year or so the patient had been cons-

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cious of some slight difficulty in breathing upon exertion. Past medical history was non-contributory except that he had had chills and fever of short duration a year previously which had been treated by his local physician. Family history and marital history were non-contributory.

Physical examination showed a well developed and nourished man in no acute distress. His temperature on the day of admission rose to 101.6 degrees F., but the pulse rate was not above 100. Examination of the head and neck revealed nothing abnormal except for poor dental hygiene. There were no petechiae in the sclerae. Examination of the lungs showed no abnormal sign. The heart was enlarged, the left border being 2.5 centimeters beyond the mid-clavicular line. There was a loud to and fro "machinery type" murmur audible all over the precordium, but maximal in the left second interspace near the sternum. The murmur had a systolic accentuation. The blood pressure at rest was 106/40 and after one minute of exercise 114/30. Examination of the abdomen revealed no abnormality. The liver and spleen were not palpable. The extremities were negative and there was no evidence of any petechiae. Laboratory examination on admission revealed a hemoglobin of 8.5 grams, a red blood cell count of 2.6 million, and a white blood count of 9,700 with 74 per cent neutrophils, 2 per cent eosinophils and 24 per cent lymphocytes. The blood smear was negative for malarial organisms. Examination of the urine and stool showed no abnormality.

Roentgenological examination of the chest on December 16, 1950, revealed no abnormality of the bony thorax. There was a marked enlargement of the heart in the transverse diameter and a prominent pulmonary conus (Figure 1). There were increased lung markings out from the hilar area, especially on the right side.

One blood culture taken on December 17, 1950, showed no growth of organisms. Due to the spiking type of temperature elevation and frequent chills the patient was started on 200,000 units of penicillin every four hours. This did not produce a dramatic response, but by the end of two weeks the temperature had settled to normal and it remained there.

Operation was done on January 11, 1951, with the patient in the lateral decubitus position. The left hemithorax was entered through the fifth intercostal space.

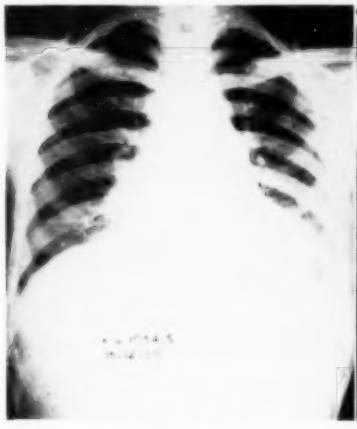

FIGURE 1

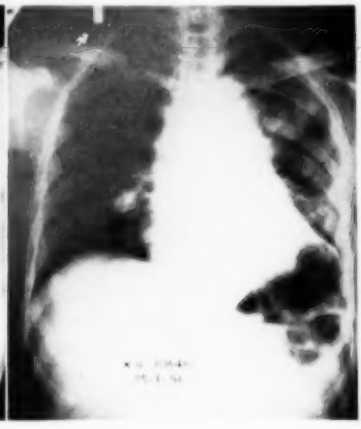

FIGURE 2

Figure 1: P-A x-ray film of chest preoperatively showing increased transverse diameter of the heart, enlarged pulmonary conus and increased vascular markings in the lung.—*Figure 2:* Postoperative x-ray film of chest 14 days after ligation of patent ductus arteriosus with probable subacute bacterial endarteritis and resection of the anterior segment of the right upper lobe.

The lung was free except over the anterior segment of the upper lobe where it was densely adherent to the chest wall and the mediastinum. The adhesions were very vascular. A mass was palpable in the anterior segment which appeared to be inflammatory and not neoplastic. The ductus was short; in fact, no length could be determined except by retracting the aorta and the pulmonary artery; both of which were enlarged. There was considerable inflammatory reaction over the ductus and the pericardium extended completely over it to the aorta. The pericardium had to be opened to mobilize the ductus safely. The ductus, when freed from the surrounding inflammatory tissue, could be stretched to about 6 mm. in length. Temporary obliteration of the ductus resulted in the heart becoming irregular even after injecting the vagus with procaine. An attempt was made three times with the same result. Therefore, 5 cc. of 1 per cent procaine were injected intravenously and a few minutes later the ductus was occluded without trouble. A purse string cotton suture was placed at each end of the ductus and a cotton transfixion suture was placed at the mid-point. A heavy silk tie was placed over this. The mediastinal pleura was closed.

It seemed unwise to leave the lesion in the upper lobe. Therefore, the anterior segment was resected after dividing the artery, vein and segmental bronchus. The chest was closed with two drains left in for drainage. The blood pressure on completion of the operation was 90/60. During the operation 3,250 cc. of blood were given. (There was considerable blood loss from the vascular adhesions).

The postoperative period was uncomplicated and the patient was discharged on January 25, 1951. Figure 2 shows the postoperative x-ray film of the chest. All the signs and symptoms of the patent ductus had disappeared.

The pathological report concerning the segment of lung as described by Dr. E. W. Gault was as follows:

Macroscopic: The specimen consists of a portion of lung (weight 53 grams) roughly pyramidal in shape with a base measuring 3 x 5 cm., and 8 cm. in height. The pleural surface is covered with some blood clot and the pleura is definitely thickened. Upon section there are two areas. Half the tissue consists of air containing lung and the other half is consolidated and pale with a well-marked line of demarcation between it and the air containing lung. At one point, at the junction of the healthy and unhealthy lung, there is some congestion.

Microscopic: Part of the lung shows the shadowy outline of the alveoli with the alveolar walls surrounding spaces filled with air and in other areas containing fibrin, red blood cells and lymphocytes with occasional granulocytes. The structure of the alveolar wall has undergone considerable change so that the endothelial nuclei cannot be seen. Some of the alveolae are filled with red blood cells. Near the edge of the infarcted area a thrombosed artery can be seen undergoing canalisation. At the edge of the infarcted area there is organizing granulation tissue containing young capillaries and fibroblasts.

Diagnosis: Organizing infarct, lung.

A communication from the referring physician states that the patient was entirely well and asymptomatic for six months after discharge. There was no recurrence of the chill and fever which he had had previously and he was engaged in his normal activities. Following some type of a domestic quarrel, he committed suicide. The referring physician learned of his death the following day by which time the body had been cremated, as is the custom here, and consequently a postmortem examination was not done.

Discussion

We have recently reported[7] two cases of persisting patent ductus arteriosus treated surgically. Since the preparation of that report an additional

four cases have been treated, one of which is the basis of this report. Five of the six patients have been cured, but one died of bronchopneumonia postoperatively. This patient was a child one and one-half years of age who had already been in congestive failure on two occasions. It has been repeatedly emphasized[6] that it is far better to wait until patients with patent ductus are at least three years of age before operating upon them, but it was the opinion of the pediatrician that the child would not survive that long without surgery. The patient had had rather extensive bronchopneumonia four weeks before operation, but the pediatrician and ourselves both believed that the pulmonary process had completely subsided before operation. Postmortem investigation, however, showed a very extensive bronchopneumonic consolidation mainly involving the right lung.

SUMMARY

1) Subacute bacterial endarteritis is not a contraindication but rather a further reason for surgical interruption of patent ductus arteriosus.

2) Since the advent of penicillin the infection can usually be controlled as a preliminary measure to surgery.

3) A case is reported in which in addition to ligation of the ductus in a patient with presumed endarteritis, a segmental lobectomy was done for an apparently chronic inflammatory process which clinically, and on pathological examination, proved to be an infarct.

RESUMEN

1) La endarteritis bacteriana subaguda no es una contraindicación sino una razón mas para la interrupción quirúrgica del ductus arteriosus.

2) Desde el advenimiento de la penicilina la infección puede habitualmente ser dominada antes de que se tratar el ductus quirúrgicamente.

3) Se relata un caso en el que ademas de la ligadura del ductus en un enfermo en quien se presumia la endarteritis, se hizo una lobectomia segmentaria por un proceso aparentemente crónico inflamatorio, que clinicamente e histológicamente demostró ser un infarto.

RESUME

1) Une endartérite infectieuse subaiguë n'est pas une contreindication mais au contraire une raison de plus d'intervenir dans les cas de persistance du canal artériel.

2) Depuis que nous avons à notre disposition la pénicilline, il est possible de juguler l'infection d'une façon courante, avant de passer à l'acte chirurgical.

3) Les auteurs rapportent une observation dans laquelle on pratiqua un traitement du canal artériel atteint vraisemblablement d'endartérite, et dans laquelle on associa une lobectomie pour une lésion apparemment chronique du poumon, qui se révéla être cliniquement un infarctus à l'examen anatomo-pathologique.

REFERENCES

1 Bullock, L. T., Jones, J. C. and Dolley, F. S.: "The Diagnosis and Effects of the Patent Ductus Arteriosus," *J. Pediat.*, 15:785, 1939.
2 Shapiro, M. J. and Keys, A.: "The Prognosis of Untreated Patent Ductus Arteriosus and the Results of Surgical Intervention," *Am. J. Med. Sc.*, 206:174, 1943.
3 Graybiel, A., Strieder, J. W. and Boyer, N. H.: "An Attempt to Obliterate the Patent Ductus Arteriosus in a Patient with Subacute Bacterial Endarteritis," *Am. Heart J.*, 15:621, 1938.
4 Gross, R. E. and Hubbard, J. P.: "Surgical Ligation of a Patent Ductus Arteriosus: Report of First Successful Case," *J.A.M.A.*, 112:729, 1939.
5 Touroff, A. S. W. and Vessell, H.: "Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus Arteriosus: Recovery Following Surgical Treatment," *J.A.M.A.*, 115:270, 1940.
6 Conklin, W. S.: "The Treatment of Patent Ductus Arteriosus," *Dis. of Chest*, 14:317, 1948.
7 Shapiro, M. J.: "Recent Advances in Surgical Treatment of Patent Ductus Arteriosus, Modern Concepts of Cardiovascular Disease," 16:1, 1947, quoted by.[6]
8 Betts, R. H. and Thomas, T.: "The Surgery of Patent Ductus Arteriosus," *J. Indian Med. Assoc.*, 20:309, 1951.

Heart Block Apparently Caused by Trauma: Report of Case

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Heart block resulting from nonpenetrating injury to the thorax is a clinical entity accepted in standard works on cardiology, yet its reported occurrence is rare. Single cases have been recorded by Rosenson,[1] Coffen, Rush and Miller[2] and Arenberg.[3] Warburg,[4] in his monograph, cited 10 cases in which there were varying degrees of atrioventricular block following injury to the thorax produced by blunt objects.

We have recently encountered a patient with heart block and Adams-Stokes disease whose condition is apparently related to previous thoracic injury. Because of the rarity of the condition we are reporting this case.

Report of Case

A 47-year-old man was first seen at the Mayo Clinic in 1943, at which time a diagnosis was made of rheumatoid spondylitis without involvement of the peripheral joints. He presented no symptoms referable to his heart, and examination of the circulatory system gave normal results. The blood pressure was 140 mm. of mercury systolic and 90 mm. diastolic; the pulse rate was 78 beats per minute. He returned in 1947 at which time the rheumatoid spondylitis was found to be inactive. Again there were no cardiac symptoms or signs of note.

In May 1949, the patient was involved in an automobile accident in which his thorax was injured when he was thrown against the steering wheel. Several ribs on the left side were fractured and pneumothorax was present. The sternum was fractured and the fragments were displaced. No penetrating wound of the thoracic wall was noted. The patient was dazed but did not lose consciousness.

Several days later the sternal fracture was openly reduced and a plate was inserted. Four months later the plate was removed. At no time during this period did the patient have any cardiac symptom and after a convalescence of several months he returned to his work as a retail grocer.

During the spring of 1951 he felt that something was wrong with his thorax. He experienced vague tightness and also precordial distress that was not anginal in nature, but he did not have dizziness or syncope. In August 1951, the patient consulted the physician in his home locality who made an electrocardiogram and informed him that he had a partial heart block with a slow pulse rate. Ephedrine sulfate was administered and he was advised to reduce the pace of his work.

On December 4, 1951, the patient felt ill at his store and went home to lie down. On arrival he experienced sudden loss of consciousness and slumped to the floor. He had no recognized seizure and promptly recovered his senses. He vomited once but soon felt normal. The following morning he awoke feeling well but when he rose from bed he again lost consciousness for a minute or two. Three days later he suddenly fell from his chair in a faint, again without warning. There were no observations of his pulse rate during these episodes.

During the next several weeks the patient did not return to work and had only limited activity about his home. On the mornings of January 17, 18 and 19, 1952, he had repeated episodes of blacking out while still lying in bed. These consisted

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of a "fading-away feeling," followed by brief generalized stiffening and then quick recovery of full consciousness. An electrocardiogram made during these attacks revealed complete heart block and extremely slow rate of ventricular beats (Figure 1).

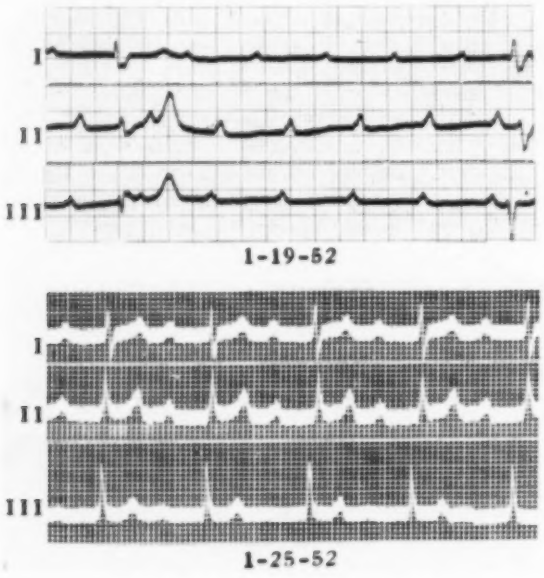

FIGURE 1: Electrocardiograms.

1-19-52: Complete atrioventricular dissociation; atrial rate 100; ventricular rate 19.
1-25-52: Partial heart block; P-R interval 0.36 second; rate 74.

The patient was examined by us on January 19, 1952. His pulse was perfectly regular and the rate was 48 beats per minute. His blood pressure was 118 mm. of mercury systolic and 70 mm. diastolic. He did not exhibit evidence of circulatory distress. The heart was not enlarged, there were no murmurs, and the lungs were clear. The remainder of his examination gave normal results except for evidence of some limitation in movements of the back.

Laboratory tests, including enumeration of leukocytes, urinalysis and determination of hemoglobin, all gave normal results. Roentgenologic examination of the thorax showed old healed fractures of the seventh, eighth and ninth ribs on the left. The cardiac outline appeared normal.

During the next 10 days repeated electrocardiographic tracings were made. These disclosed disturbances in atrioventricular conduction varying from complete atrioventricular dissociation to prolongation of the P-R interval ranging from 0.28 to 0.38 seconds. When heart block of first degree was present, the heart rate varied from 74 to 86 beats per minute. No other significant abnormalities were noted in the tracings. During this 10 day period of observation he received no treatment other than rest in bed. No further episodes of loss of consciousness occurred while he was in the hospital. Administration of 1/60 grain (1 mg.) of atropine sulfate had no effect on the delayed atrioventricular conduction. He was dismissed with a guarded prognosis and was advised to limit sharply his activities.

The patient was seen again two months later, when he reported that he had been resting at home. No further faintness, syncope or seizures had been experienced

and he had felt well except for soreness about the margins of the ribs. He had determined his pulse rate several times daily and had never found it to be less than 70 beats per minute. Examination of the patient disclosed no evident change from his previous condition. No abnormalities were seen in the electrocardiogram except a P-R interval of 0.28 seconds.

Comment

Traumatic cardiac disease associated with nonpenetrating injuries to the thorax has been of mounting interest in the past few decades, in which there has been an ever-increasing incidence of thoracic trauma and a greater use of electrocardiography. A blow against the thorax or sudden thoracic compression may give rise to a wide variety of cardiac disturbances ranging from transient harmless arrhythmia to ventricular fibrillation and sudden death; it may also be the cause of pericarditis or of myocardial contusion accompanied by a clinical picture resembling that produced by myocardial infarction. Rupture of valves and sudden or delayed rupture of the chambers of the heart may also occur.

Clinical and experimental evidence discloses that almost any type of arrhythmia may be the result of trauma. Kissane, Fidler and Koons[5] produced heart block in anesthetized dogs by heavy blows on the thoracic wall. The most frequent lesion produced was subendocardial and subpericardial hemorrhage. Hearts examined two months after such trauma showed myocardial scarring.

It may be assumed that in cases of traumatic heart block the anatomic basis is deep-seated hemorrhage, edema and scarring in the region of the bundle of His. The difficulty of the exact localization of this structure in man is well known.

In our case there was a latent period of more than two years between the time of injury and the discovery of heart block by means of electrocardiography. However, examinations before the injury had all given normal results and no other likely etiologic factor was evident. There is no actual proof that the injury caused the heart block but it certainly was the most likely cause. This patient is 47 years of age and it may be argued that his heart block could be due to coronary disease. This is a possibility but he is fairly young to have heart block on the basis of coronary sclerosis with no other symptom of coronary disease.

The patient has rheumatoid spondylitis and it may be considered that the heart block could occur because of this. We have not seen a case of complete heart block that has been proved to be the result of spondylitis. In Rosenson's case the block was discovered soon after injury. It was of transient nature and three months later the electrocardiogram showed normal atrioventricular conduction. In the case of Coffen and associates, as in ours, electrocardiographic proof of the block was delayed, but the block was apparently complete and permanent, having been present for 18 years when it was reported. Arenberg's patient was examined 18 months after injury and at that time a slow irregular pulse was noted. Two months later there was electrocardiographic proof of complete heart block.

It is increasingly apparent that cardiac damage may occur at the time

of thoracic injury and may go unrecognized, either because of roentgenogram which discloses no abnormalities is deemed to be sufficient examination or because the injury to the heart may be overshadowed by the presence of such conditions as a bony injury or a collapsed lung. The electrocardiograph should be employed more frequently in cases of thoracic injury, and it must be remembered that the heart is not perfectly protected by the wall of the thorax.

SUMMARY

A case of heart block and Adams-Stokes disease apparently resulting from nonpenetrating trauma to the thorax is reported. It is recommended that electrocardiography be employed more frequently as a part of the examination following thoracic injury so that damage to the heart may be detected early.

RESUMEN

Se refiere un caso de bloqueo del corazón y de enfermedad de Adams-Stokes que aparentemente consecutivo a un traumatismo no penetrante del tórax. Se recomienda que se emplée la electrocardiografía mas frecuentemente como parte del examen después de los traumas en el torax de modo que el daño cardiaco pueda ser descubierto precozmente.

RESUME

Les auteurs rapportent un cas de bloc du coeur avec maladie d'Adams-Stokes qui semble résulter d'un traumatisme non pénétrant du thorax. Ils suggèrent d'employer plus fréquemment l'électrocardiographie comme un élément de l'examen qui doit être fait à la suite d'un traumatisme thoracique. Ainsi la lésion cardiaque pourra être découverte précocément.

REFERENCES

1 Rosenson, William: "Heart Block in a Child of Ten Years Following Trauma to the Pericardium," *Am. J. Dis. Child.*, 28:594, 1924.
2 Coffen, T. H., Rush, H. P. and Miller, R. F.: "Traumatic Complete Heart Block of Eighteen Years Duration: With Review of Literature," *Northwest Med.*, 40:195, 1941.
3 Arenberg, H.: "Traumatic Heart Disease; A Clinical Study of 250 Cases of Nonpenetrating Chest Injuries and Their Relation to Cardiac Disability," *Ann. Int. Med.*, 19:326, 1943.
4 Warburg, Erik: "Subacute and Chronic Pericardial and Myocardial Lesions Due to Non-penetrating Traumatic Injuries," London, Oxford University Press, 1938, page 147.
5 Kissane, R. W., Fidler, R. S. and Koons, R. A.: "Electrocardiographic Changes Following External Chest Injury to Dogs," *Ann. Int. Med.*, 11:907, 1937.

The Effects of Rapid Changes of Altitude on Patients Undergoing Pneumotherapy

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That flying involves at least a theoretical hazard to individuals with closed pneumothorax has long been known. Many observers have made references to the simple application of Boyle's law, concerning the reciprocal relationship of volume and pressure of gases. In 1942 Lovelace and Hinshaw[2] reported a roentgenographic demonstration of the effect of altitude on a series of patients, utilizing a low-pressure chamber rather than an airplane. Their pictures demonstrate definite enlargement of pneumothorax space, in rough proportion to decreased barometric pressure (simulated increase of altitude). They conclude, in part, that "it would appear to be extremely important to determine whether or not the calculated expansion of pneumothorax during flight actually occurs or whether expansion is restrained and relative positive pressure develops."

In an effort to settle this point and with the broader object of arriving at a rational basis for decision as to which patients undergoing pneumotherapy could fly with safety and which could not, a series of experiments was carried out. (The generic term "pneumotherapy" includes patients with unilateral or bilateral pneumothorax, pneumoperitoneum, and combinations of these procedures with other forms of collapse therapy).

The initial study consisted in reading intrapleural and intraperitoneal pressures at the top and bottom of a 25 story elevator shaft—a vertical distance of 294 feet, before and after refills. The theoretical difference in pressure, as customarily recorded in cm. of water on the manometer of a pneumothorax apparatus, would be approximately 10 cm. This was checked by recording the pressure in a liter bottle connected to a water manometer, and found to be correct. An anaeroid barometer rose approximately 0.25 inches (Hg.) during the descent. Patient A, an otherwise healthy young woman who had been receiving pneumoperitoneum for approximately two and a half years for moderately advanced bilateral tuberculosis, then entered the elevator on the top floor to receive a routine weekly refill. Her intraperitoneal pressure was +12+13. Before the administration of air the elevator was taken to the ground floor, where the manometer reading was +11+12. (It should theoretically have been +2+3). After receiving 700 cc. of air, the pressure rose to +16+17. On returning to the top floor, it was found that instead of the theoretical rise in pressure of 10 cm., the manometer still showed +16+17 cm.

The experiment was repeated with patient B, likewise a young woman, clinically well, who had been receiving left pneumothorax for six months for a minimal lesion. The initial pressure on the 26th floor was 0–4, and it was unaltered by the descent to the first floor. At this point a routine weekly refill of 400 cc., with the patient still lying comfortably in the prone

position, produced a reading of +4—2, and this pressure likewise remained unchanged during and after the ascent to the top floor.

A few weeks before this, patient B had been taken to an altitude of 10,000 feet in a small, non-pressurized plane. Twenty minutes were spent in the ascent, an average rate of climb of 500 feet per minute. The altitude was maintained for 10 minutes, during five of which she performed mild to moderate exercise. No discomfort was experienced and she exhibited surprisingly little dyspnea. This flight occurred three and a half days after a routine weekly refill.

For the next test a larger, but non-pressurized airplane was used. The

TABLE I

(Descent columns should be read from the bottom up)

Altimeter Readings	PATIENT A Intraperitoneal Readings Plus 9/750/Plus 10 (take-off five minutes after completion of refill)	PATIENT B Intrapleural Readings 350/Plus 2-4 (take-off five minutes after completion of refill	Barometer Readings	Pressure in Sealed Bottle
Sea-level	+10	+2-2	30.4	
1,000 feet	+14	+2-4	29.4	+ 33
2,000 feet	+13	+2-4	28.6	+ 66
3,000 feet	+13	+2-4	27.5	+ 99
4,000 feet	+13	+2-4		+130
5,000 feet	+15	+3-3	25.8	+162
6,000 feet	+15½	+3-3	25.1	+192
7,000 feet	+16	+4-2	24.25	+219
8,000 feet	+17½	+4-2	23.65	+248
9,000 feet	+18	+4-4	23.05	+275
10,000 feet	+20	+4½-3	22.5	+302

TABLE III: INTRAPLEURAL PRESSURES

(Descent column should be read from the bottom up)

	PATIENT C		PATIENT D		PATIENT G		PATIENT I		PATIENT H	
	Ascent	Descent	Ascent	Descent	Ascent	Descent	Ascent	Descent	Ascent	Descent
Sea-level	0-5	—3-6	—3-6	—4-8	—1-5	—2-8	+4-3	+5-2	+4-4	+3-6
2,000 ft.	+1-5	—3-5	—3-8	—4-8	0-5	—2-8	+4-3	50 -2-8	+1-6*	+3-6
4,000 ft.	+2-5	—1-6	—2-7	—3-8	+1-5	—1-7	+2-8	—1-6	+3-4	+3-6
6,000 ft.	+3-5	+1-6	—1-7	—3-8	+1-4	—1-6	+5-9	+2-4	+3-4	+3-5
8,000 ft.	+4-3	+3-4	0-6	0-6	+3-3	—1-5	+6-12	+3-5	+4-5	+4-3
10,000 ft.	+6-2		+2-4		+2-3		+9-13		+4-3	

*No explanation for this unusual reading, except that patient was unduly apprehensive and breathing irregularly.

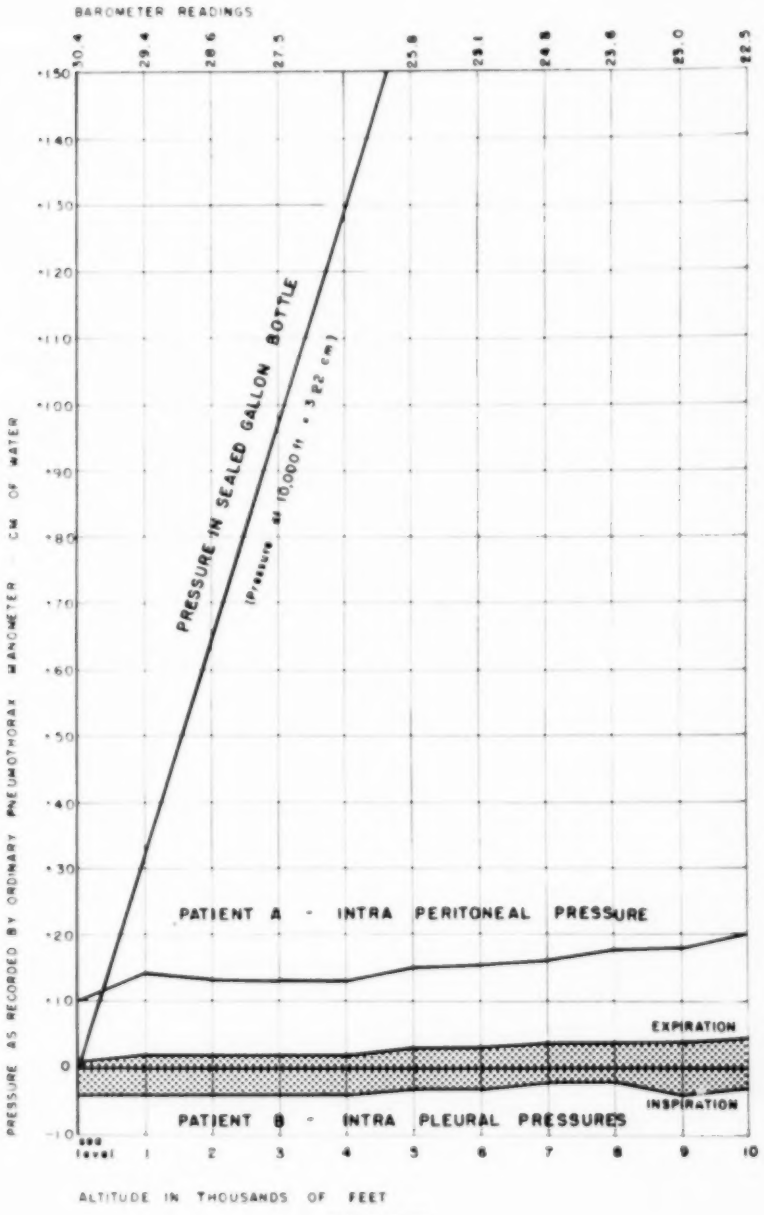
BAROMETER READINGS
30.4
29.4
28.6
27.5
25.8
23.1
24.8
23.6
23.0
22.5
+150
+140
+130
+120
+110
+100
+90
+80
+70
+60
+50
+40
+30
+20
+10
0
-10
PRESSURE AS RECORDED BY ORDINARY PNEUMOTHORAX MANOMETER - CM OF WATER
PRESSURE IN SEALED GALLON BOTTLE
(Pressure at 10,000 ft = 322 cm)
PATIENT A - INTRA PERITONEAL PRESSURE
EXPIRATION
INSPIRATION
PATIENT B - INTRA PLEURAL PRESSURES
Sea level
1
2
3
4
5
6
7
8
9
10
ALTITUDE IN THOUSANDS OF FEET

TABLE II

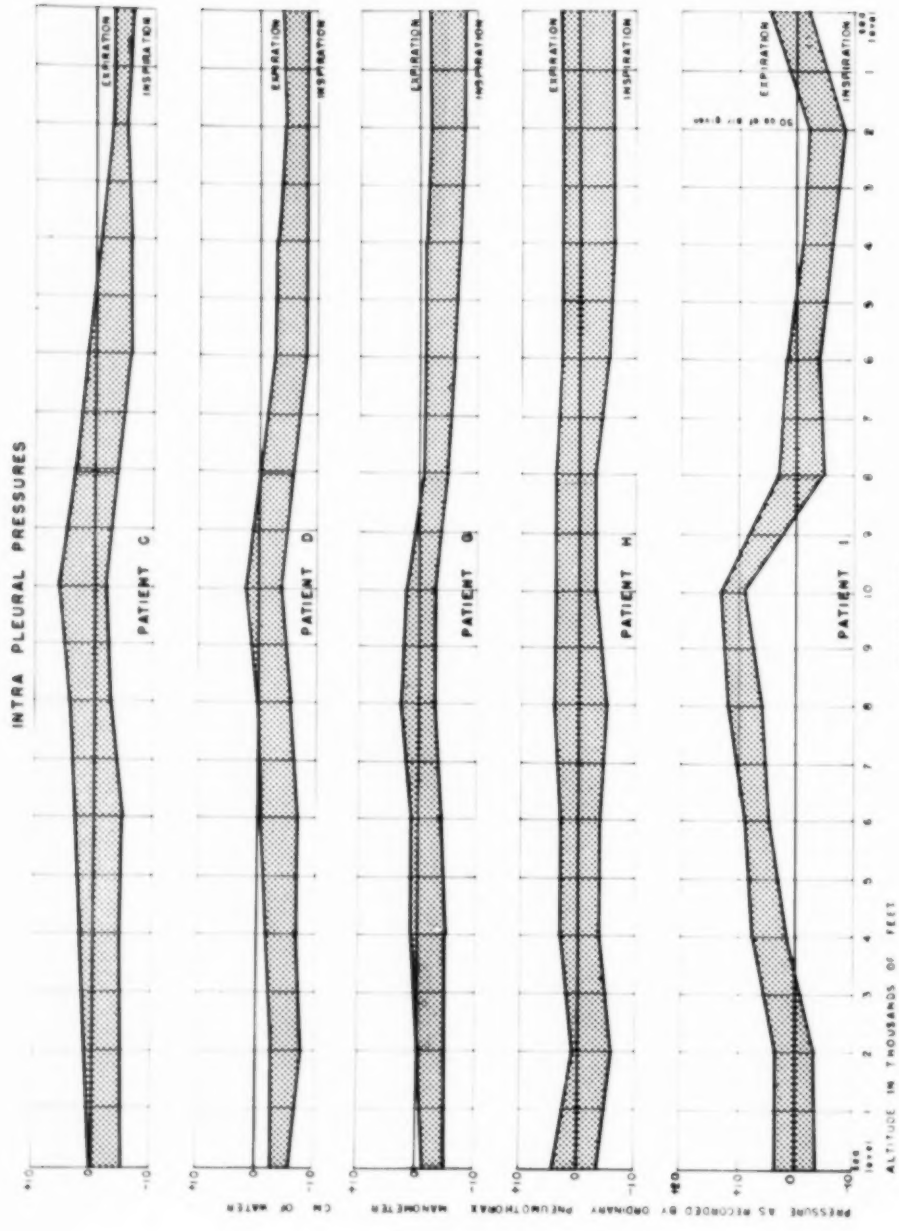
INTRA PLEURAL PRESSURES
PATIENT C
PATIENT D
PATIENT G
PATIENT H
PATIENT I
EXPIRATION
INSPIRATION
+10
0
-10
CM OF WATER
MANOMETER
PNEUMOTHORAX
ORDINARY
PRESSURE AS RECORDED BY
ALTITUDE IN THOUSANDS OF FEET

TABLE IV

same two patients were given routine refills in the plane at sea-level. Patient A (pneumoperitoneum) lay in the supine position, but patient B (pneumothorax, left) sat up in a comfortable armchair. Pressure readings were recorded at each 1,000 feet of elevation, up to an altitude of 10,000 feet. The results are given in tabular and graphic forms in Tables I and II.

The theoretical increase in the pressure in the air-tight gallon bottle should have been some 322 cm. of water. That the recorded increase was about 20 cm. less is doubtless accounted for by the marked fall in temperature within the plane between sea-level and 10,000 feet. The pneumoperitoneum pressures are recorded as single figures because on quiet respiration the oscillations were less than 1 cm. In the case of patient A, after leveling off at each thousand feet, the pressure fell one or two cm. before further ascent began. Associated with the fall of pressure after leveling off, there was definite diminution of dyspnea. This phenomenon was probably due to diffusion and redistribution of air to the far reaches of the abdominal cavity. Patient B expressed no complaint except slight dyspnea above 6,000 feet. This symptom was shared by both operators.

It seemed established that regardless of theoretical considerations, these two girls could fly without either discomfort or danger as long as the altitude did not exceed 10,000 feet. Fluoroscopic examinations before and after each experiment showed the usual amounts of collapse. Ten thousand feet was selected as the critical altitude for several reasons. Large modern airplanes are pressurized so that the pressure never falls below the normal pressure at 8,000 feet, so that anyone who can safely tolerate an altitude 25 per cent higher than this, can certainly fly around the world. Smaller, non-pressurized commercial planes seldom exceed 10,000 feet for more than brief periods, and when they do both passengers and crew are supposed to be supplied with oxygen.

To broaden the base of this study, the last experiment was repeated with ten patients in a low-pressure chamber. The purpose of giving refills immediately before "ascent" was of course to make conditions as unfavorable as possible. Patients A and B were included in the group. A brief description of the remaining eight might be of interest.

TABLE V: INTRAPERITONEAL PRESSURES

(Descent column should be read from the bottom up)

	PATIENT A		PATIENT E		PATIENT F	
	Ascent	Descent	Ascent	Descent	Ascent	Descent
Sea-level	+9	+9	+6	+4	+12	+9
2,000 feet	+10	+9	+6	+4	+12	+8
4,000 feet	+11	+10	+8	+6	+12	+10
6,000 feet	+11	+12	+8	+7	+14	+11
8,000 feet	+14	+12	+9	+8	+15	+15
10,000 feet	+18		+10		+17	

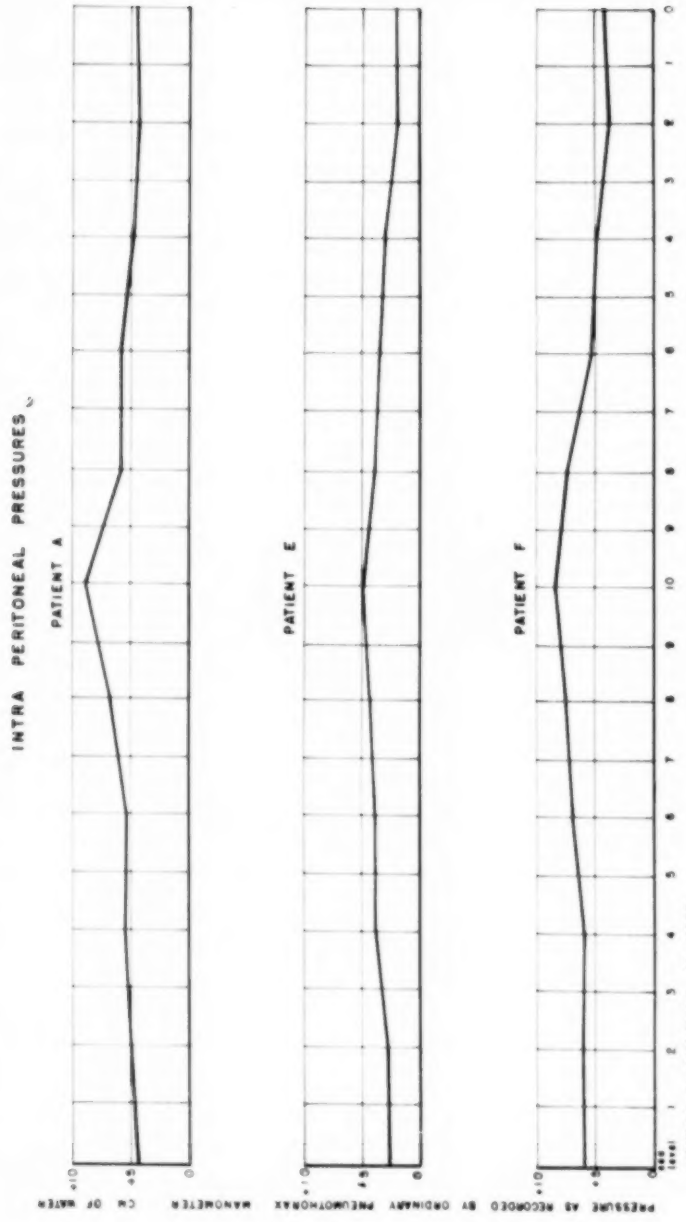
INTRA PERITONEAL PRESSURES
PATIENT A
PATIENT E
PATIENT F
MANOMETER CM OF WATER
PRESSURE AS RECORDED BY ORDINARY PNEUMOTHORAX
ALTITUDE IN THOUSANDS OF FEET
Level

TABLE VI

Patient C. An otherwise healthy young woman; left pneumothorax of six months' duration, for minimal tuberculosis.

Patient D. Undernourished, easily fatigued young woman; right pneumothorax of three years' duration for moderately advanced disease.

Patient E. An otherwise healthy, middle-aged woman; pneumoperitoneum of five years' duration for far advanced bilateral disease. Sputum cultures intermittently positive, concentrated smears negative for four years.

Patient F. An otherwise healthy young woman; right thoracoplasty (five ribs) 18 months before; pneumoperitoneum for two and a half years for far advanced bilateral disease.

Patient G. An otherwise healthy young woman; left pneumothorax for 18 months for moderately advanced disease.

Patient H. An otherwise healthy young woman; paraffin plombage, right, four years ago; left pneumothorax of three and a half years' duration for far advanced disease.

Patient I. An otherwise healthy, middle-aged woman; left hydropneumothorax of 22 years' duration for far advanced tuberculosis; well and working for 20 years; came to California 15 years ago with a non-expansile left lung; fluid thin, sterile.

Patient J. An otherwise healthy young man; bilateral pneumothorax of three and a half (left) and three years' (right) duration for far advanced tuberculosis.

The patients ranged in age from 25 to 45 ("middle aged" means at least 35). Eight of these 10 were engaged in their usual occupations, one (patient C) had only been home from the sanatorium for three weeks, and one (patient D) was doing only light work.

"Ascent" in the chamber was at the rate of about 2,000 feet per minute, and "descent" at 3,000 feet per minute. These rates were diminished when patients complained of discomfort in their ears. The chamber accommodated two patients at a time, except that patient J was taken alone because he had a needle in each pleural space, and patient B was taken alone because she had volunteered to ascend to 18,000 feet. It is interesting that

TABLE VII: PATIENT J — INTRAPLEURAL PRESSURES

(Descent column should be read from the bottom up)

	LEFT		RIGHT	
	Ascent	Descent	Ascent	Descent
Sea-level	+2-4	+2-8	+3-7	+3-9
2,000 feet	+4-5	+4-6	+3-7	+3-9
4,000 feet	+6-6	+5-6	+5-8	+3-8
6,000 feet	+7-6	+6-5	+5-8	+4-7
8,000 feet	+8-5	+8-6	+5-8	+5-8
10,000 feet	+13-4*		+8-8*	

*Increased excursion and more-than-expected increase of post-expiratory pressure doubtless attributable to severe ear pain.

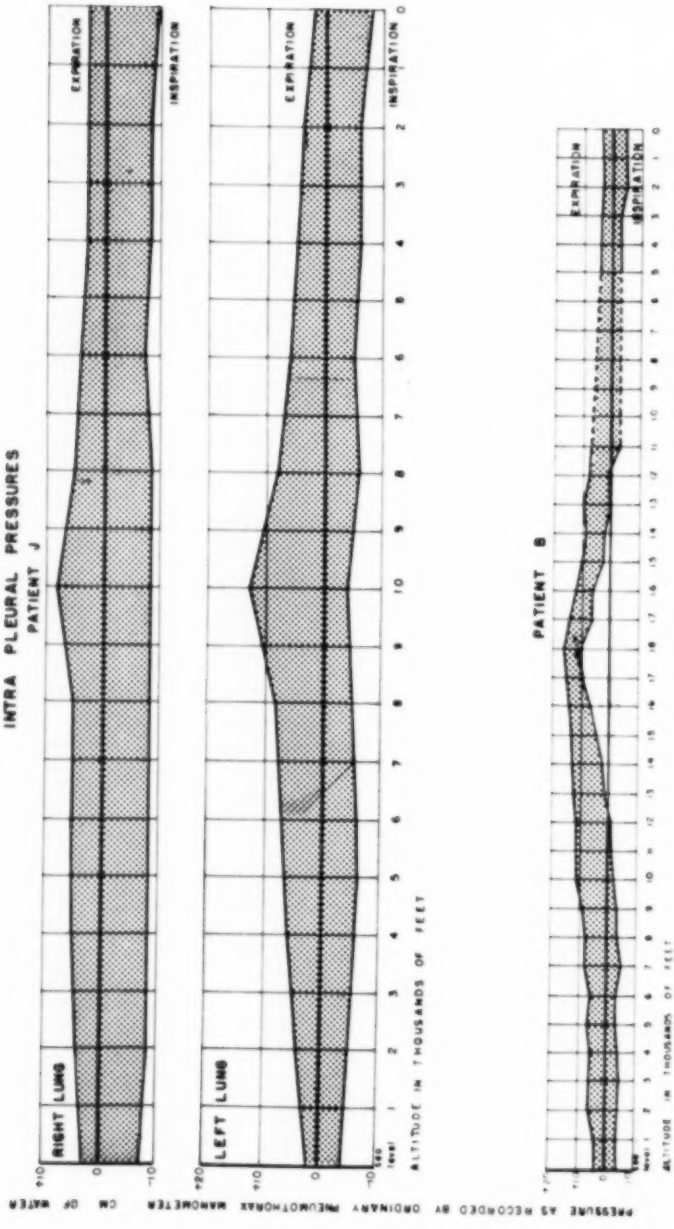
INTRA PLEURAL PRESSURES
PATIENT J
RIGHT LUNG
LEFT LUNG
EXPIRATION
INSPIRATION
ALTITUDE IN THOUSANDS OF FEET
PATIENT B
PRESSURE AS RECORDED BY ORDINARY PNEUMOTHORAX MANOMETER CM OF WATER

TABLE VIII

the pressures during descent showed a definite tendency to be lower than the pressures at corresponding altitudes during ascent. (In the case of patient I it was necessary to administer 50 cc. of air between 2,000 feet and sea-level to restore her pre-ascent pressure. This is the average amount of her refills at three-weekly intervals. She alone received no air prior to ascent, having been filled a few days before). Several possible explanations of this phenomenon naturally come to mind:—relatively rapid (and irreversible) absorption of air from the pneumo space to compensate for the pressure differential, "stretching" of the space, again due to pressure differential, etc.

The hiatus in the record of patient B in the descent from 11,000 feet to 5,000 feet is due to the fact that in attempting to clear her Eustachian tubes, she blew all the water out of the manometer. This permitted the escape of some air from her pneumothorax, but the manometer was refilled and the status quo ante was restored at 5,000 feet.

TABLE IX: PATIENT B — INTRAPLEURAL PRESSURES

(Descent column should be read from the bottom up)

	Ascent	Descent
Sea-level	+4-4	+3-5
1,000 feet	+4-4	+3-5
2,000 feet	+6-4	+3-5
3,000 feet	+6-4	+4-3
4,000 feet	+6-4	+4-3
5,000 feet	+7-3	+2-4 300 +4-3
6,000 feet	+6-3	
7,000 feet	+8-4	
8,000 feet	+8-3	
9,000 feet	+9-3	
10,000 feet	+10-2	
11,000 feet	+11-1	+7-3†
12,000 feet	+11-1	+8+1
13,000 feet	+12+1	+10,0*
14,000 feet	+13+2	+9+2
15,000 feet	+13+4	+10+3
16,000 feet	+14+7	+12+6
17,000 feet	+15+9	+14+6
18,000 feet	+16+10	

*Increased excursion and increased post-expiratory pressure doubtless due to severe ear pain.

†At this point patient requested (and was granted) permission to attempt to clear her Eustachian tubes. See text above for results.

The actual figures are shown in Tables III, V, VII and IX and in the graphs in Tables IV, VI and VIII. It should be borne in mind that a rigid container will show a rise in pressure of 322 cm. of water between sea-level and 10,000 feet, and a rise of 517 cm. between sea-level and 18,000 feet.

Lovelace and Hinshaw,[1-3] Gellenthien,[4] Rabino,[5] Margaria, Talenti and Reviglio,[6] Dowd,[7] and numerous others have stressed the theoretical hazards of flying to patients undergoing pneumotherapy, and in several instances have cited actual cases, some with fatal outcome. On Dowd's case an autopsy failed to establish the cause of death. It would appear, either from their direct statements or by implication, that all of these workers are impressed by the applicability of Boyle's law.

Acknowledgments: The author is greatly indebted to Dr. John H. Lawrence and his staff at the Donner Laboratory, University of California, for the use of the low-pressure chamber; to Frank W. Fuller, Jr. for his services as pilot and for the use of his airplane; to Dr. G. N. Pierce for recording the pressures on approximately half of the patients, and most of all to the 10 patients who kindly cooperated in this study.

SUMMARY

1) Boyle's law is not applicable to the behavior of air in the pleural or peritoneal cavities of patients undergoing pneumotherapy. Reasons why this is true are suggested.

2) Ten patients with assorted forms of permanent and temporary collapse were all able to tolerate an altitude of 10,000 feet without discomfort or significant symptoms. One patient with unilateral pneumothorax remained symptom free at 18,000 feet even without oxygen.

3) It may be reasonably anticipated that ambulatory pneumotherapy patients who are free of dyspnea at sea-level may fly without restriction and without oxygen in modern pressurized airplanes.

RESUMEN

1) La ley de Boyle no es aplicable al comportamiento del aire en las cavidades pleural y peritoneal en los enfermos sujetos a neumoterapia. Las razones a que esto se debe y por qué ella es así, se sugieren.

2) Diez enfermos con formas diversas de colapso permanente y temporal fueron todos capaces de tolerar una altitud de 10,000 pies sin molestias o síntomas significativos. Un enfermo con neumotorax unilateral a 18,000 pies no tuvo síntoma alguno aun sin oxigeno.

3) Puede decirse razonablemente que los enfermos ambulatorios con neumoterapia que no experimentan disnea al nivel del mar, pueden volar sin restricción y sin oxígeno en los aviones modernos con presión del aire compensada.

RESUME

1) La loi de Boyle n'est pas applicable au comportement de l'air dans les cavités pleurales et péritonéales en ce qui concerne les malades soumis à une thérapeutique gazeuse. L'auteur suggère des arguments à l'appui de cette thèse.

2) Dix malades atteints de formes diverses, traités par collapsothérapie permanente ou temporaire furent tous capables de supporter une altitude de 10,000 pieds sans gêne ni symptômes significatifs. Une malade avec pneumothorax unilatéral resta sans manifester aucun symptôme à 18,000 pieds, et sans le secours de l'oxygène.

3) On peut raisonnablement penser que les malades porteurs de pneumothorax ou de pneumoperitoneum ambulatoire et qui sont indemnes de dyspnée au niveau de la mer peuvent effectuer des voyages en avion sans le secours de l'oxygène dans les avions modernes "pressurisés."

REFERENCES

1 Lovelace, W. R. II and Hargreaves, J.: "Transportation of Patients by Airplane," *J. Aviation Med.*, 13:2, 1942.
2 Lovelace, W. R. II and Hinshaw, H. C.: "Dangers of Aerial Transportation to Persons with Pneumothorax; Roentgenographic Demonstration of the Effect of Decreased Barometric (High Altitude) and of Increased Barometric Pressure," *J.A.M.A.*, 118:1275, 1942.
3 Lovelace, W. R. II and Hinshaw, H. C.: "Aerial Transportation of Patients," *War Med.*, 2:580, 1942.
4 Gellenthien, C. H.: "Altitude and Artificial Pneumothorax," *J.A.M.A.*, 114:727, 1940.
5 Rabino, A.: "Pericoli Dei Viaggi Aerei Durante La Cura Pneumothoracicia," *Minerva Med.*, 9:624, 1929.
6 Margaria, R., Talenti, C. and Reviglio, G. M.: "Modificazioni Indotte Dalla Depressione Barometrica Sul Pneumothorace; Studio Sperimentale Radiologico," *Minerva Med.*, 9:637, 1929.
7 Dowd, K. E.: "Report of Death of Passenger Under Treatment by Pneumothorax," *Av. Med.*, ¿?:346, 1945.

Peritoneal Effusions in Pneumoperitoneum Treatment with Antihistaminics

A Preliminary Report

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Among the authors[1-7] who have discussed the matter of abdominal fluid in pneumoperitoneum therapy, there seems to be general agreement about the importance of this complication. The incidence is low and when fluid does appear, it is of little clinical significance as it is usually not considerable in amount. The fluid is often unassociated with symptoms and will absorb after a variable period of time without interference with the pneumoperitoneum. In these cases refills are continued in the usual way or less air may be given.

There is unanimity of feeling that only an occasional pneumoperitoneum has fluid of such degree or type as to require discontinuation of therapy. In these instances the fluid is usually considerable and causes pressure symptoms such as fullness or pain in the abdomen and back and dyspnea. In addition, the patient may be acutely ill with fever, sweats, malaise, nausea, vomiting and diarrhea. These patients (besides receiving less air) require aspiration of fluid with the paracenteses repeated as often as necessary. On rare occasions the paracenteses will not control the situation as the fluid keeps reforming and the pneumoperitoneum has to be discontinued. In these individuals peritonitis is usually present and peritoneal adhesions may also be evident.

In the usual case, the fluid is clear, serous, and without tubercle bacilli. Pathologically, there may be some thickening of the peritoneum though the inflammatory change may be minimal and normal peritoneum may be present with the fluid. In tuberculous peritonitis, tubercle bacilli are in the fluid, the exudate may be purulent and the peritoneum usually has typical inflammatory findings.

There has been little written concerning the etiology of abdominal fluid associated with pneumoperitoneum therapy. We have seen no report describing the use of antihistaminics in pneumoperitoneum effusions. Antihistaminics have been employed in the treatment of pulmonary tuberculosis. Judd and Henderson[8] have described much improvement from antihistaminics in patients with reinfection tuberculous pneumonia and exudative lesions.

We have used antihistaminics in four patients who had considerable abdominal fluid develop while undergoing pneumoperitoneum therapy.

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This medication was suggested by one of us (J.O.) when the abdominal fluid revealed a high percentage of eosinophiles and therefore the possibility of allergic origin. In subsequent taps examinations for eosinophilic cells (by modification of the Wright stain recommended by Dr. J. Stanely Woolley*) revealed a high percentage of these cells in three of the cases.

Case Reports

Case 1: E.L., a 16-year-old white female was admitted to the Municipal Sanatorium November 3, 1949, with a moderately advanced pulmonary lesion. Sputum concentrates were positive for tubercle bacilli. Pneumoperitoneum was initiated January 9, 1950. During January and February 1950, refills were given twice a week and averaged 1,000 cc. Early in March 1950, a small amount of abdominal fluid was noted. The refills were then diminished to 700 cc. weekly. This regimen was continued until the first abdominal paracentesis in September 1950. The fluid remained at the level of the inferior third of the fourth lumbar vertebra during March 1950, and in April it was almost gone, but in May it increased again reaching the 12th dorsal vertebra. Because of the considerable amount of fluid, abdominal paracentesis was done September 14, 1950 and 3,900 cc. of cloudy serous yellow fluid was removed and replaced with 4,500 cc. of air. Figure 1 shows the level of the fluid just prior to the first abdominal tap. After this tap a small amount of fluid remained. Refills (500 to 800 cc.) were given weekly during the latter half of September. The fluid again increased in amount and abdominal aspirations were done three times during October. On October 5, 2,200 cc. of fluid was removed and 2,000 cc. of air injected. Some fluid remained after this tap, and on October 10, 2,700 cc. of fluid was taken out and replaced with 3,000 cc. air. The peritoneal cavity appeared free from fluid after this paracentesis but it reappeared in a few days. Another tap on October 17 yielded 400 cc. of fluid (with 1,000 cc. air replacement) and little fluid remained. After this paracentesis, the condition remained unchanged for several weeks. A refill of 800 cc. of air was given November 8, 1950. The fluid continued to reform and by November 13, 1950 reached the top of the 12th dorsal vertebra. Figure 2 shows the condition after these four paracenteses. The fluid level is now only a trifle lower than prior to the first tap. Mercuhydrin was administered (2 cc. intramuscularly twice a week) between November 14 and December 8, 1950 with no diminution of fluid. Another abdominal tap was done November 24, 1950 and 1,600 cc. of cloudy, yellow serous fluid was removed and 1,000 cc. of air given. The fluid had a specific gravity of 1.022, cell count of 825 per cu. mm. and total protein of 4.8 gm./100 cc. The differential count revealed principally lymphocytes and eosinophiles with 36 per cent of the former and 36 per cent of the latter. Concentration, culture and animal inoculation for tuberculosis were negative. Within five days after the tap, the fluid was back to the level of November 24, 1950. Another paracenteses was done December 5, 1950 with 1,750 cc. fluid removed and 1,000 cc. air replacement. The fluid was similar in character to that of November 24, 1950, with specific gravity of 1,018, 1,015 cells per cu. mm., 5 grams total protein per 100 cc., no tubercle bacilli, and a differential count of 44 per cent lymphocytes and 39 per cent eosinophiles. The abdominal fluid reformed rapidly and another aspiration was done December 8, 1950 with 2,400 cc. fluid removed and 1,200 cc. air replacement. The character of the fluid was unchanged with 31 per cent lymphocytes and 50 per cent eosinophiles. After this paracentesis the abdomen was almost free of fluid. Pyribenzamine (50 mg. four times a day) was given from December 15 to 17, inclusive. Thephorin was then substituted, 25 mg. four times a day, after December 20, 1950 and continued. Only a small amount of fluid reappeared during this period. Because of this, air refills were started again after mid December. There seemed to be an association

*Head of Laboratory.

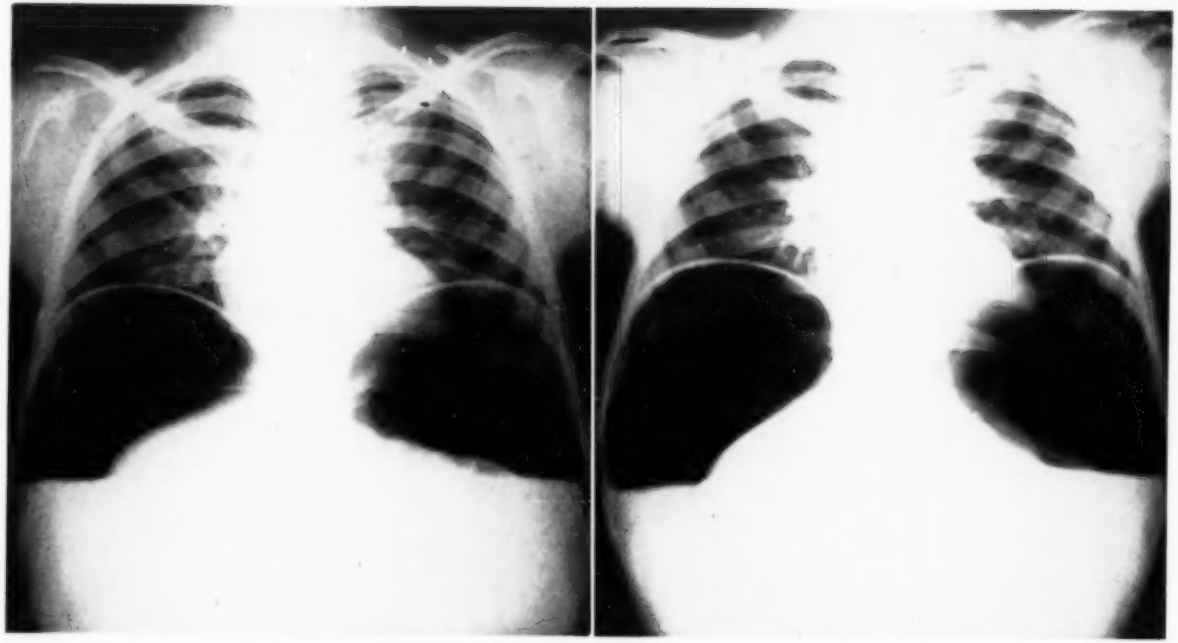

FIGURE 1

FIGURE 2

Figure 1: September 7, 1950. Pneumoperitoneum initiated January 9, 1950. Abdominal fluid had first appeared in March 1950, and persisted. This is the picture prior to the first abdominal tap which was done September 14, 1950. — *Figure 2:* November 13, 1950. Between the date of Figure 1 and this picture, the patient had had four abdominal paracenteses. However, the fluid kept reforming after each tap.

between the lack of reformation of the fluid and the Thephorin. To study this correlation more closely, the Thephorin was stopped on January 29, 1951. At that time there was only a small amount of fluid present but it increased rapidly in a few days. The level then diminished slightly during the next week but in another week (by February 16, 1951) had increased to a point eight inches above the iliac crest. Another paracentesis was done February 16, 1951, with removal of 2,650 cc. of fluid and 1,600 cc. air replacement. The character of the fluid remained unchanged (cloudy, serous, yellowish; 600 cells and 4.3 gm. protein; negative for tubercle bacilli and a differential count of 37 per cent lymphocytes and 43 per cent eosinophiles with a scattering of segmented and nonsegmented cells and macrophages). There was no fluid in the abdomen following this tap and Thephorin was again administered (50 mg. four times a day). This medication was continued until June 20, 1951. Only a small amount of fluid reformed under this regimen. Refills were again given, averaging 800 cc. every 10 days. This status continued without much change until the patient's discharge from the Sanatorium on August 18, 1951. The fluid remained small in amount and had shown only a slight increase after the antihistaminics were stopped.

The patient's general condition remained quite good throughout. The fluid rarely caused symptoms and only when of marked degree, resulted in abdominal discomfort or backache.

All sputum concentrates after March 1950 were negative and all cultures were negative (except September and October, 1950). Cavity closure and much resolution of the infiltration occurred with the pneumoperitoneum and only residual fibrosis remained.

Other laboratory findings (aside from examination of abdominal fluid) were essentially negative. The blood count was within normal range, with no increase of eosinophiles (eosinophilia of 3 per cent or less in all blood counts, although in one specimen it was 5 per cent). Blood chemistry done October 27, 1950, when abdominal paracenteses were frequent showed 460 mg. chlorides and 6.6 gm. total protein with 3.6 gm. albumin and 3 gm. globulin. The urine on occasion showed a trace of albumin and a few WBC but all cultures for tuberculosis were negative.

Allergic work-up with sensitization tests revealed a moderate reaction to cucumber and slight reaction to several other foods. A slightly positive test was found with a few inhalants.

The patient had been on an ambulatory status since March 28, 1951, and was assigned to the rehabilitation program with a daily work tolerance of 1 hour on May 3, 1951. She was discharged on August 18, 1951, with a diagnosis of chronic pulmonary tuberculosis, inactive, and pneumoperitoneum. She was on a daily work tolerance of four hours. The fluid had remained small in amount and pneumoperitoneum refills were continued (800 cc. every seven days) without difficulty.

Case 2: M.A.H., a 23-year-old white female was admitted to the Municipal Sanatorium June 10, 1948. On admission the diagnosis was moderately advanced pulmonary tuberculosis. Sputum cultures were positive. Pneumoperitoneum was initiated December 8, 1949. During the first two months refills of 1,000 cc. were given twice a week. From February to July 1950, when abdominal fluid first appeared, air was given weekly. The fluid level was maintained quite constantly. Then through mid-September 1950, the refills averaged 800 cc. a week. Right phrenic nerve crush was performed August 26, 1950. Fluid was visible at the level of the upper margin of the 12th dorsal vertebra. The first paracentesis was done October 2, 1950, with removal of 5,300 cc. of cluody, serous, yellow fluid and replacement with 6,000 cc. of air. The fluid reformed readily and on October 10, 1950, 1,500 cc. was removed with air replacement of 1,500 cc. The fluid continued to build up and on October 17, 1950, another 2,700 cc. was removed with 3,000 cc. air replacement. After this aspiration the fluid was below the iliac crest. However, within a week, she complained of dyspnea, and abdominal discomfort and tight-

ness. A reducible but painful umbilical hernia was also present. This umbilical hernia had become apparent about two months after pneumoperitoneum was initiated. The pneumoperitoneum space was deflated with removal of 1,500 cc. of air on October 23, 1950. Another paracentesis was done November 8, 1950, with removal of 6,000 cc. of fluid and replacement by 400 cc. of air. The cloudy, serous, yellow fluid had a specific gravity of 1.022, 460 cells per cu. mm., 4 gm. total protein and was negative for acid fast bacilli (on concentration, culture and animal inoculation) and negative for other organisms by culture. The differential count revealed 17 per cent polymorphonuclears, 14 per cent macrophages, 24 per cent eosinophiles and 45 per cent lymphocytes. The fluid reformed slowly and during the month, after the last aspiration, three refills of 800 cc. of air were given. She was comfortable and by the end of November only a small amount of fluid was present. However, by mid-December 1950 the fluid had increased to the level of the mid-portion of the 11th dorsal vertebra. In spite of four abdominal paracenteses, which had been done after fluid first appeared, the fluid level was higher than before the first tap. Another abdominal paracentesis was performed December 15, 1950, with removal of 4,700 cc. fluid and replacement with 3,000 cc. air. This fluid was similar in character to that of November 8, 1950. After this tap, practically no fluid was discernible in the abdomen. Antihistaminics were started December 14, 1950, with pyribenzamine 50 mg. four times a day. This was continued to December 19, 1950, when Thephorin, 25 mg. four times a day, was sub-

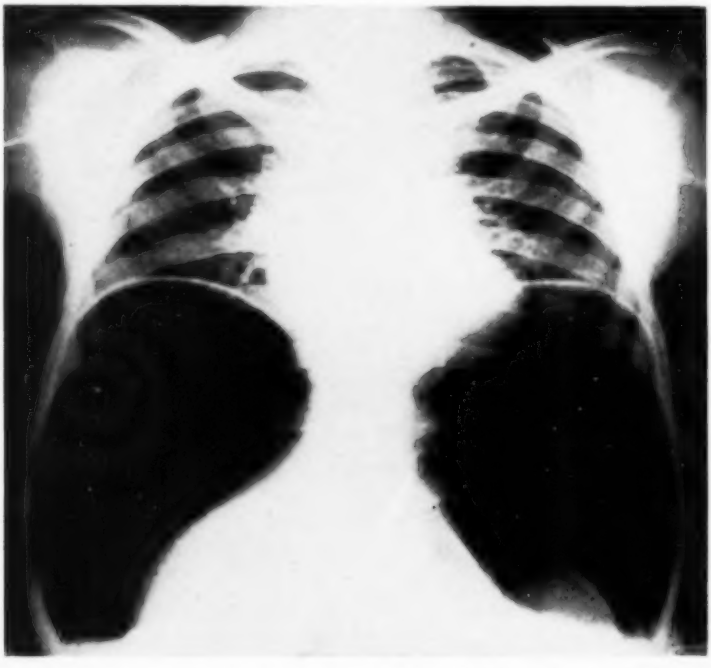

FIGURE 3, Case 1: January 19, 1951. After the last paracentesis on December 8, 1950, the pneumoperitoneum space was almost free of fluid. Antihistaminic therapy was then begun. This film shows the condition after five weeks of antihistaminic therapy. No paracenteses have been done and a small amount of fluid has reformed. The diaphragms are at the level of the seventh posterior rib. The fluid is at the level of the upper margin of the first lumbar vertebra.

stituted because she complained of excessive drowsiness. This medication apparently was of value as there was no increase in fluid by fluoroscopic observation. To determine if the Thephorin was responsible for the fluid not reforming, it was purposely stopped on January 19, 1951. There was a rapid reaccumulation of fluid with an increase noted within four days. On January 23, 1951, 4,600 cc. of fluid was removed and 3,600 cc. of air injected. Air refills were not given again after this date. The fluid showed little change compared to previous specimens. After this paracentesis some fluid remained in the abdomen (three inches above iliac crest) and Thephorin, 25 mg. four times a day, was restarted. The fluid again did not increase. Thephorin was again stopped on January 29, 1951. The fluid at first showed minor changes, increasing and decreasing slightly. However, there was a general rise in the level and Thephorin was restarted February 14, 1951, using 50 mg. four times a day. On February 16, 1951, the patient had discomfort and the fluid level reached nine and one-half inches above the iliac crest. Abdominal tap was done the same day with removal of 6,250 cc. of fluid and no air replacement. The fluid was cloudy, serous, amber, with 1,016 specific gravity, 900 cell count, 4.7 gm. protein, no bacteria, and a differential count of 10 per cent polymorphonuclears, 42 per cent lymphocytes, 38 per cent eosinophiles and 10 per cent macrophages. The eosinophile count was higher in this fluid than in any of the other specimens. Following the paracentesis of February 16, 1951, there was no abdominal fluid visible and Thephorin was continued. The large pneumoperitoneum pocket is outlined clearly by x-ray film with no fluid present. Fluoroscopic observations showed that fluid did not reform when antihistaminics were being administered but increased when medication was stopped. She felt comfortable but the umbilical hernia was tense and herniorrhaphy was done February 21, 1951. At this time no abdominal fluid was present. The peritoneum appeared thickened. The surgical specimen was reported as "normal umbilical hernia sac; chronic inflammation of the omentum." After the herniorrhaphy pneumoperitoneum was discontinued. The space began to diminish and only a small amount of fluid reformed. By February 28, 1951, the pneumoperitoneum space was small. The diaphragms dropped to the level of the 10th rib posteriorly. The abdominal organs were also moving upwards. The final abdominal tap was done March 3, 1951, with removal of 550 cc. fluid with no air replacement. The fluid was cloudy, serous, amber, with specific gravity of 1,022 and 1,350 cells, 4.8 gm. protein, no bacteria and a differential count of 29 per cent polymorphonuclears, 64 per cent lymphocytes, 4 per cent eosinophiles and 3 per cent macrophages. The drop in eosinophiles was considerable. Figure 3 is the picture 12 days after the umbilical herniorrhaphy. Fluid has formed to an extent considerably less than when no antihistaminics were administered. The umbilical herniorrhaphy wound healed by primary intention. Thephorin was continued until April 5, 1951. By May 3, 1951, there was no pneumoperitoneum or fluid visible. She became ambulatory on May 9, 1951, and was assigned to the rehabilitation program with a daily work tolerance of one hour on June 15, 1951.

Gastric cultures were persistently positive until April 1949. From October 1950, the cultures have been negative persistently. Five urine cultures were negative for tubercle bacilli. Blood counts were normal and the eosinophile count on all occassions was less than 4 per cent with one exception, February 1951, when 7 per cent was found. Blood chemistry (November 1950) revealed no abnormal findings.

Allergic testing revealed moderate reaction to apple and slight positive reactions for several other foods. Moderate sensitivity was present to feathers and cottonseed, while several inhalants were slightly positive.

Her condition continued to be excellent. She was discharged on September 15, 1951, with a diagnosis of chronic pulmonary tuberculosis, inactive, and pneumoperitoneum with a daily work tolerance of four hours. The pulmonary lesion (with slight bilateral upper lobe fibrosis) remained stable. The abdominal picture continued unchanged.

Case 3: B.B., a 37-year-old male Negro was admitted to the Municipal Sanatorium January 1, 1950, with far advanced chronic pulmonary tuberculosis. Sputum concentrates were persistently positive for tubercle bacilli. Pneumoperitoneum was initiated June 30, 1950. The first two weeks refills of 800 cc. were given every seven days and the following month they averaged 1,000 cc. Through the end of September, about 1,150 cc. were administered every four to seven days. By October 5 the diaphragm was at the level of the superior margin of the 10th rib posteriorly and abdominal fluid was visible at the level of the upper margin of the fourth lumbar vertebra. Refills had been reduced during the first part of October to 700 cc. and during the latter part of the month to 500 cc. From then until the end of December, only 300 to 700 cc. of air were given every two weeks. At the end of October some discomfort was present and he had pain in the abdomen and back. On October 23, 1950, abdominal tap was done and 4,500 cc. clear amber fluid was removed with no air given. He was comfortable after this paracentesis which removed all of the fluid. By mid-November 1950, fluid had reformed and was one and one-half inches above the iliac crest though he had no symptom. On November 29, 1950, right phrenic crush was done. The fluid had increased to the level of the top of the first lumbar vertebra. On December 30, 1950, 2,600 cc. fluid was removed and 1,200 cc. air injected. This fluid was cloudy, serous, yellowish with a specific gravity of 1,022, 1,150 cells per cu. mm., 5.6 gm. protein per 100 cc. and the bacteriology was negative. The differential count revealed 19 per cent segmented cells, 22 per cent lymphocytes, 14 per cent macrophages and 45 per cent eosinophiles. On January 3, 1951, the fluid on the right side of the abdomen was at the level of the top of the 12th dorsal spine and on the left side at mid-level of first lumbar vertebra. On January 10, 1951, Thephorin, 25 mg., twice daily was started and three days later the dose was increased to four times a day. Another paracentesis was done January 19, 1951, and 1,500 cc. fluid was removed and 1,200 cc. air injected. This fluid was cloudy, serous, yellowish, with 1,200 cells, negative for tubercle bacilli and other pathogens and with a differential count of 45 per cent lymphocytes, 14 per cent polymorphonuclear, 32 per cent macrophages and 9 per cent eosinophiles. After the tap the fluid remained at a level of about two and one-half inches above the iliac crest. From January 24 to 31, 1951, benadryl was used instead of Thephorin. On February 1, 1951, antihistaminics were stopped. The fluid increased slowly and on February 26, 1951, the level was seven and one-half inches above the iliac crest and he complained of discomfort. Paracentesis was done February 26, 1951, with removal of 2,300 cc. fluid and replacement with 1,000 cc. of air. This fluid was cloudy, serous, yellowish, with no bacteria and a differential count of 20 per cent segmented cells, 3 per cent non-segmented, 30 per cent lymphocytes, 22 per cent macrophages, and 25 per cent eosinophiles. The abdominal cavity was almost dry after the tap. Antihistaminics were restarted on February 26, 1951, with 25 mg. Thephorin four times daily. The next day the dose was increased to 150 mg. daily and on March 28, 1951, to 200 mg. By March 13, 1951, fluid had reformed and was four and one-half inches above the iliac crest. Small weekly refills (500 to 800 cc.) were started in March. By March 31, 1951, the fluid had increased, but he was comfortable and refills were continued. The fluid increased slowly and by May 4, 1951, was five inches above the iliac crest or at the level of the top margin of the second lumbar vertebra. By June 1, 1951, the fluid had increased even more and was eight inches above the iliac crest. This took place even though Thephorin was being continued. The antihistaminic was stopped June 22, 1951. With pneumoperitoneum the pulmonary cavities were markedly reduced in size. The sputum concentrates were converted but the cultures remained persistently positive. In view of the persistent pulmonary cavitation and difficulty with the pneumoperitoneum, the treatment was stopped and pulmonary surgery was recommended.

Allergic tests revealed considerable sensitivity, especially in the inhalant group. Moderate reaction was obtained to timothy and orchard grass, dust, feathers, and

alterneria and hormodendron. Marked sensitivity was present to lima beans and moderate reaction to apples, with slight sensitivity to a few other foods.

Case 4: B.M., a 27-year-old Negro female, was admitted to the Municipal Sanatorium March 2, 1950, with a moderately advanced lesion. Sputum was persistently positive for tubercle bacilli. Pneumoperitoneum was induced April 6, 1950. Until mid-June 1950, refills averaged 1,000 cc. twice a week. From then until December 1950, 1,000 cc. of air was given once a week. On December 24, 1950, she developed fever up to 102 degrees F. and pain in the right shoulder. Fever persisted and by December 28, 1950, headache and diarrhea were present and she appeared toxic. On December 28, 1950, a small amount of fluid was first seen in the abdomen but it absorbed in a few days. Streptomycin, in daily gram doses, was started December 29, 1950, and given for 42 days. PAS, 10 grams daily, was given with the streptomycin and continued until April 4, 1951. The fluid appeared again in greater amount January 5, 1951. She continued to complain of headache, malaise and diarrhea until January 9, 1951. No regular air refills were given after the fluid appeared. The temperature remained close to 102 degrees F. until the end of January. It then fell slowly, reaching normal by mid-February and continuing normal thereafter.

Pyribenzamine was started on January 8, 1951, with 50 mg. three times daily, given for five days. Benadryl was substituted for the pyribenzamine, using 25 mg. three times daily, and 50 mg. at night. On January 16, 1951, 50 mg. of Thephorin was given daily in addition. Benadryl was stopped January 13, 1951, and Thephorin on February 28, 1951.

On January 16, 1951, 4,000 cc. of fluid was removed and 2,500 cc. of air administered. The fluid was cloudy, serous, yellowish, with a specific gravity of 1,022, a cell count of 1,700, total protein of 4.8 gm., and negative for tubercle bacilli. However, culture and animal inoculation for tuberculosis were later positive. The differential count revealed 34 per cent segmented cells, 16 per cent non-segmented, 48 per cent lymphocytes and 2 per cent macrophages. This aspiration did not remove all of the fluid. On January 19, 1951, fluid was at the level of the superior margins of the left 12th dorsal spine and right first lumbar vertebra. She was fairly comfortable at this time. However, the fluid persisted and in a few days abdominal discomfort and backache appeared. On January 27, 1951, 3,900 cc. fluid was removed with no air replacement. The fluid was cloudy, serous, greenish with a specific gravity of 1,020 and 980 cells, 4.3 gm. protein and negative for organisms. The differential count showed 14 per cent segmented cells, 3 per cent non-segmented, 73 per cent lymphocytes, 4 per cent macrophages and 6 per cent eosinophiles. A roentgenogram taken January 30, 1951 revealed several abdominal fluid levels. On the left side of the abdomen there was fluid at level of mid-12th dorsal vertebra. However, on the right side, the fluid was encapsulated in a large pocket just below the diaphragm with fluid at the level of the ninth dorsal vertebra and a small pocket with fluid at level of the 12th dorsal vertebra. On February 6, 1951, 2,350 cc. of fluid was aspirated. This specimen was cloudy, serous, yellowish with specific gravity of 1,020, 1,250 cells, and 4 gm. protein. Differential count revealed 19 per cent segmented cells, 1 per cent non-segmented, 67 per cent lymphocytes, 3 per cent macrophages and 10 per cent eosinophiles. On February 7, 1951, the fluid on the left side of abdomen was at the upper margin of the 12th dorsal vertebra, and the fluid pockets on the right side were smaller in size. No further paracenteses were done and no air was given and the patient continued to feel quite well. On April 10, 1951, no more abdominal air or fluid was visible. Only a fibrotic residue of infiltration was present between the second and fourth anterior interspaces.

The urine was negative. There was slight leucocytosis during the febrile period with an increase in non-segmented cells. The eosinophile count was normal in all blood counts except once on January 30, 1951, when 12 per cent was found. A later

blood count was normal. The sputum concentrates had been converted by April 1950, and remained persistently negative thereafter. All cultures have been negative aside from one positive report in June 1950. Excellent resolution of the pulmonary infiltration occurred with the pneumoperitoneum. She became ambulatory March 28, 1951. Excellent clinical progress continued and she was assigned to the rehabilitation program May 3, 1951. She was discharged on August 18, 1951, with a daily work tolerance of four hours and clinical status classified as inactive. The lung picture remained stabilized and the abdomen continued clear of fluid.

Discussion

In evaluation of any treatment for pneumoperitoneum effusions, it must be kept in mind that either (a) the fluid may absorb spontaneously, or (b) after one or more abdominal paracenteses, it may no longer reform. Before an agent is considered to be of therapeutic value in handling pneumoperitoneum fluid, it must be certain that improvement probably will not occur without it. Our observations are only of a preliminary nature as so few cases are reported, results were not uniformly successful and all patients had paracenteses before medication.

Antihistaminics apparently do not influence the absorption of the fluid. There was no decrease in the amount of fluid while Thephorin alone was given. However, the drug seemed to be of value in keeping the fluid from reforming. In these four patients the plan of treatment was to remove as much fluid as possible and continue to use the antihistaminic. It was found that in the first two patients the Thephorin seemed to be the factor in preventing fluid formation, while in the third, it was of practically no influence, and in the fourth, it was definitely of no value. There seemed to be no relationship between the value of the antihistaminic and changes in the eosinophilia of the fluid.

In case four, with tubercle bacilli in the fluid, the antihistaminic was definitely of no help. In a study of all of our pneumoperitoneum cases with abdominal fluid (to be reported by I.D.B.) it was found that when an acute clinical course was associated with the fluid containing tubercle bacilli, pneumoperitoneum invariably had to be discontinued.

After the abdomen has been tapped dry as possible, at least 200 mg. of Thephorin should be given daily. This can be continued for many weeks. We were not troubled with side reactions.

Fluid in all cases had the characteristics of an exudate and presumably was inflammatory in origin. The etiology of the fluid in these pneumoperitoneum patients is not known. Physical factors such as irritation of the peritoneum by air or pressure of the air on the veins or lymphatics may be involved. Certainly the cause can be inflammatory and an active tuberculous peritonitis may be present as in case four. Tubercle bacilli may infect the peritoneum by way of the lymphatics, lymph nodes or blood stream, or locally from adjacent structures.

How much of the fluid formation is on an allergic basis is not definite. The cause of the eosinophilia in the fluid is not understood. In a recent excellent discussion of pleural fluid eosinophilia,[9] the diseases and conditions associated with this phenomenon were enumerated. Danzig and Pope[10]

have reported that pleural eosinophilia may be associated with pulmonary emboli and hemorrhagic pleural effusion. As in pleural fluids, the effusion in pneumoperitoneum may be due to many factors. It may be a manifestation of an allergic reaction to a number of antigens including tuberculosis. The most plausible explanation for the presence of eosinophilia in pleural or peritoneal effusions is a hypersensitive response.

Woolley[11] has suggested that "peritoneal effusions may be due to a protein-like material which has appeared in the fluid (escape from intestinal lymphatics?) to which the peritoneum has become sensitized and to which it finally reacts, with the irritation manifesting itself as an effusion. This is reasoning by analogy from what takes place when a specific antigen is introduced into the pleural space and comes in contact with the sensitized pleural cell (vide tuberculosis)."

The exact nature by which the antihistaminics influence the formation of fluid is not clear.

No clinical allergy was present in any of these patients but sensitization tests were positive in all of them to various foods and inhalants.

The antihistaminics have, therefore, limited value in the treatment of pneumoperitoneum fluid. However, abdominal fluid can, in a small number of pneumoperitoneum cases, be a problem of considerable magnitude and any effective therapeutic regimen would be of clinical importance. For this reason this preliminary report with discussion of only a few cases has been presented.

SUMMARY

Four cases of pneumoperitoneum complicated by considerable abdominal fluid have been presented. Repeated paracenteses alone failed to control the condition as fluid reformed rapidly and to a marked degree. When removal of abdominal fluid was combined with the use of an antihistaminic, in two of the four patients, only a small amount of fluid reformed. In the other two patients, the antihistaminic was of no value and fluid reaccumulated.

RESUMEN

Se han presentado cuatro casos de neumoperitoneo complicados con un considerable liquido abdominal. Las paracentesis reiteradas no lograron corregir estas condiciones puesto que el liquido se volvia a reunir rapidamente y en un volumen marcado. Cuando la extracción del liquido se combinó con el uso de un antihistamínico en dos de los cuatro enfermos, solo una pequeña cantidad de liquido volvió a reunirse. En los otros dos enfermos el antihistamínico no fué de valor y el liquido volvió a acumularse.

RESUME

Les auteurs rapportent quatre cas de pneumopéritoine compliqué d'une ascite importante. Les ponctions répétées furent incapables à elles seules d'empêcher l'épanchement de se reproduire rapidement, et d'une façon considérable. Chez deux des quatre malades, lorsqu'on combina l'évacuation de l'ascite à l'usage d'un antihistaminique, il ne se reproduisit qu'une

petite quantité de liquide. Chez les deux autres malades, l'action de l'antihistaminique fut nulle et l'épanchement se reproduisit.

REFERENCES

1 Rilance, Arnold B. and Warring, Frederick C. Jr.: "Pneumoperitoneum Supplementing Phrenic Paralysis," *Am. Rev. Tuberc.*, 44:323, 1941.
2 Fowler, W. O.: "Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 44:474, 1941.
3 Banyai, Andrew L.: "Pneumoperitoneum Treatment," C. V. Mosby Co., St. Louis, 1946.
4 Trimble, H. G., Eaton, I. L., Crenshaw, G. O. and Gourley, I.: "Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 57:433, 1948.
5 Morris, Everett: "Induced Pneumoperitoneum in the Treatment of Advanced Pulmonary Tuberculosis in Children," *Dis. of Chest*, 12:121, 1946.
6 Moyer, R. E.: "Pneumoperitoneum and Phreniclasia in the Treatment of Pulmonary Tuberculosis," *Dis. of Chest*, 15:43, 1949.
7 Calix, A. and Jacobs, S.: "Pneumoperitoneum," *Dis. of Chest*, 14:233, 1948.
8 Judd, A. R. and Henderson, A. R.: "Antihistaminics in Human Tuberculosis," *Ann. Allergy*, 7:306, 1949.
9 MacMurray, F. G., Katz, S. and Zimmerman, H. J.: "Pleural Fluid Eosinophilia," *New Eng. J. Med.*, 243:330, 1950.
10 Danzig, L. E. and Pope, R. H.: "Pleural Eosinophilia with Special Reference to Its Association with Pulmonary Emboli," *Am. Pract.*, 2:254, 1951.
11 Woolley, J. S.: Personal communication.

The Problem of Anaesthesia for Thoracoplasty

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In the earlier years of the operation of thoracoplasty speed was the primary aim of the surgeon in order that shock and poisoning by toxic general anaesthetics should be kept to a minimum. Presently there was a revolt against this outlook and the operation came to be conducted in more leisurely fashion under local anaesthesia. This change made accurate dissection possible and produced a genuine reduction both in mortality and in the frequency of extension of the disease in the immediate post-operative period. It did not, however, abolish these accidents, nor did they disappear even when operations were carried out on patients to whom streptomycin was being given.[2,3] Further, unless sedatives were given in so great doses that the cough reflex was abolished for long periods the performance of the operation under local anaesthesia involved the infliction of a considerable amount of pain and discomfort on the patients. Since the other advantages of local anaesthesia for thoracoplasty, viz., quiet respiration and an avascular field, can readily be produced by modern methods of general anaesthesia it will be seen that the sole justification for the retention of relatively barbarous techniques of anaesthesia for thoracoplasty must lie in their influence on mortality and spread rate, and it is primarily with these that the present paper is concerned.

Pilot Study

A pilot study of the various available methods of anaesthesia for thoracoplasty was first carried out to discover, if it were possible, a technique having the following desiderata. First, its use must be associated with an immediate recovery of consciousness and of the cough reflex at the end of the operation. Secondly, the agents employed must be non-inflammable; for the electrocoagulation was regularly to be used by the surgeon. Thirdly, the technique must not permit the development of hyperpnoea, because overbreathing always increases the amount of paradoxical respiration consequent upon decostalisation. An adequate oxygen supply, and in the cases where the available aveolar surface was reduced, even an oxygen rich mixture, must be provided without upsetting the anaesthesia. It was later realized that it should be possible also to control the respiration whenever the exigences of the operation demanded it. At the time of the pilot series, however, this was not considered essential and simple positive pressure was relied upon to keep the lung sufficiently expanded when the pleura was breached or when a very extensive mobilization of the apex was performed.

In this pilot study the anaesthetic methods noted in Table I were employed. At first various general anaesthetic techniques were tried but no

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consistently reliable and satisfactory method was found. In the few instances where an induction dose of Pentothal followed by nitrous oxide and oxygen alone gave adequate anaesthesia without hyperpnoea and coughing, the results were ideal. But in a large proportion of the cases where this method was tried the patients coughed either while their ribs were being cleared or while the apex was being mobilized. Some supplement to the nitrous oxide was then necessary. Chloroform was rightly or wrongly considered to be too dangerous; so trichlorethylene was given instead for the purpose. It proved unsatisfactory because of the frequent development of congestion and cyanosis. Additional doses of Pentothal were satisfactory as a supplement where the difficulty was the patient's reacting to painful stimuli but as would be expected this drug was useless for the control of coughing. Further, both the patients who received large doses of additional Pentothal and those to whom trichlorethylene was given were all slow to recover consciousness. The administration of trichlorethylene with oxygen only after a Pentothal, nitrous oxide and oxygen induction gave complete control of the cough reflex and entirely abolished the cyanosis but with this technique the recovery of consciousness was even more delayed than with those tried previously. Further, cardiac irregularities during the anaesthesia were disquietingly common. It therefore seemed at that time that a satisfactory non-inflammable general anaesthetic for thoracoplasty was not available. The possibilities of local anaesthesia were next explored. In a series of 20 cases brachial plexus and paravertebral block were combined with infiltration of the operation area but all the difficulties mentioned earlier in this paper were encountered and this technique seemed little better than any of the others. In fact, the return of spontaneous coughing after the operation was, because of the large amounts of opiate required, even more delayed than in patients operated on under general anaesthesia.

About the time that local anaesthesia was being tried and found wanting, the author began to be able to obtain supplies of curare, first in the form of "Intocostrin" and later as solutions of the alkaloid d-tubocurarine.

TABLE I: The Anaesthetic Techniques Used in the Pilot Series.

Induction Agent	Maintenance Agent	Supplement	No. of Cases
Pentothal	N_2O-O_2	Pentothal	7
Pentothal	N_2O-O_2	Trilene	19
Pentothal	Trilene	—	9
Local	Omnopon Scopolamine	(N_2O-O_2 in 6 cases only)	20
Pentothal	Pentothal	Curare	3
Pentothal	N_2O-O_2	Curare	33
Pentothal	N_2O-O_2	—	20
N_2O-O_2	N_2O-O_2	Curare	1
		TOTAL:	112

He noticed during abdominal operations that patients who were being curarized became unable to cough long before respiration became seriously depressed. Since the frequent appearance of coughing and hyperpnoea during nitrous oxide and oxygen anaesthesia had caused this method to be regarded as unsuitable for thoracoplasty, it seemed that curare might be given in quantity sufficient to prevent these untoward symptoms, yet be without adverse effect on all the advantages of this form of anaesthesia. The last cases of the pilot series were conducted with the aid of this drug and both surgeon and anaesthetist were most pleased with the outcome. The problem of finding a consistently reliable technique of general anaesthesia for thoracoplasty seemed to have been solved and it remained only to examine the results in a large series of cases to see whether the greater comfort afforded to patient, surgeon and anaesthetist alike was purchased at the cost of a greater mortality or post-operative spread rate.

The Main Series

The ideal method of solving the problem set out at the end of the last paragraph would obviously have been a controlled series in which alternate unselected patients were operated on under local and general anaesthesia. It was felt, however, that an investigation of the kind was not feasible since there had already been difficulty in persuading patients to submit

TABLE II: The Numbers and Types of Stages Performed (Main Series).

Stage	Extent of Operation	No. Performed
Upper Posterior	Ribs 1, 2 and 3 resected, occasionally part of 4; sometimes scapulectomy; sometimes apicolysis.	99
Second Posterior	Ribs 4, 5 and 6 resected. Occasional scapulectomy.	72
Third Posterior	Ribs 7, 8 and where required, 9 resected.	32
Antero-lateral	Ribs 2, 3, 4 and often 5 resected from the front.	45
Other	Mostly revision operation or laying open empyema cavity.	11
	TOTAL:	259

TABLE III: The State of the Patients Before Operation.

Unilateral Disease	51 cases
Healed Contralateral Tuberculosis	7 cases
Active Contralateral Tuberculosis	59 cases
No Information (Service cases whose records were not available)	9 cases
TOTAL:	126 cases

TABLE IV: Mortality After Thoracoplasty Under Different Forms of Anaesthesia.

Author	Country of Origin	Date of Study	Type of Anaesthesia	Number of Cases	Number of Operations	Number of Deaths	Mortality — Per cent Per Patient	Mortality — Per cent Per Operation
Holmes Sellors[5]	England	1936-46	Not stated	633	—	17	2.7	—
McHale[2]	England	1948	Local	85	209	3	3.5	1.4
Millar[4]	England	1946-47	Local	204	382	8	4.0	2.1
Price Thomas and Cleland[6]	England	1937-40	Local	72	—	3	4.1	—
Hagn-Meincke[7]	Denmark	1935-41	Local	424	801	40	9.4	5.0
Gilbert[8]	Canada	1937-48	Spinal	—	575	23	—	4.0
Kinsella et al.[2]	U.S.A.	1922-43	Mostly Local	613	1574	34	5.55	2.16
Parke et al.[9]	U.S.A.	1932-47	158 Local 647 General	367	805	27	7.4	3.4
Pilot Series		1944-47	20 Local 92 General	—	112	3	—	2.7
Present Series		1947-49	General	126	259	1	0.8	0.4

to operation under local anaesthesia while the pilot study was being made. Fortunately there have recently been published the results of two series in other English Sanatoria where local anaesthesia was used, in one instance for a group of rather better risk patients than those of the present series[4] and in another for a group of rather poorer risks.[2] It is felt that these cases afford an adequate control for the present study.

The present series of cases comprises all the anaesthetics given by the author for thoracoplasty in an English sanatorium from July 1, 1947 to December 31, 1949. In every case anaesthesia was induced with Pentothal or Kemithal (sodium cyclohexenyl allyl barbiturate) and maintained with nitrous oxide and oxygen. In a few cases a small additional dose of barbiturate was given if the patient reacted on the skin incision but no more was given thereafter. Curare was injected when necessary in amount sufficient to control coughing and prevent hyperpnoea. At first endotracheal intubation was performed only when difficulty with secretion was anticipated. It was feared that its routine use would be associated with the development of tuberculous laryngitis or with the exacerbation of any lesions already present. When it became apparent that this complication was amenable to treatment with streptomycin the possibility of its appearance ceased to cause anxiety and intubation began to be performed as a routine. In fact, tubes have been passed on patients known to have tuberculous lesions of the larynx and even without prophylactic streptomycin

TABLE V: The Incidence of Serious Spread After Thoracoplasty Under Local and General Anaesthesia. (Recent English figures only.)

Author	Type of Anaesthesia	No. of Cases	No. of Operations	No. of Spreads	Frequency of Spread Pct. per Patient	Frequency of Spread Pct. per Operation
McHale	Local	85*	209	5	5.9	2.4
Millar	Local	204	382	9	4.4	2.3
Present Series	General	126†	259	4	3.2	1.5

* Includes some cases done under streptomycin umbrella.
† Includes only one case done under streptomycin umbrella.

TABLE VI: Distribution of the Various Types of Spread in Present Series.

Serious Spreads:	
Massive Bronchopneumonic Extension	3 cases
Less Extensive Bronchopneumonic Extension	1 case
Other Spreads:	
Reactivation Previously Quiescent Disease in Contralateral Lung	4 cases
Progress of Pre-existing Active Disease in Opposite Lung	3 cases
Progress of Disease in Same Lung	1 case
TOTAL:	12 cases

no ill effect has been observed at subsequent laryngoscopy. Two other modifications have been made in the originally adopted technique. First bronchoscopic tracheobronchial toilet is now performed at the conclusion of any operation in the course of which sputum has been aspirated from the trachea. It must, however, be admitted that in two patients of the series bronchopneumonic spread appeared in spite of this precaution. Secondly, blood has become more readily available and it is now given routinely to patients undergoing all but the most minor stages, in quantity sufficient to make good the estimated blood loss.

In all 259 anaesthetics have been given to 126 patients. The actual number of the different stages will be found in Table II. In all but five cases the lateral position was used for posterior stages. The type of patient to whom thoracoplasty has been offered has changed during the time of this series but similar changes in outlook took place in other centres simultaneously. Bilateral disease was not regarded as a contra-indication to the operation which was performed in the presence of artificial pneumothorax or pneumoperitoneum which had been induced to control contralateral disease (Table III).

TABLE VII: The Comparative Incidence of All "Spreads" After Thoracoplasty.

Author	Type of Anaesthesia	No. of Cases	No. of Operations	No. of Spreads	Frequency of Spread Pct. per Patient	Frequency of Spread Pct. per Operation
Parke et al.[9] (Whites only)	158 Local 657 General	367	805	81	22	10
Yang and Lees[10]	Mostly General plus local infiltration	317	1388	34	10.7	2.5
Present Series	General with Curare	126	259	12	9.5	4.6

TABLE VIII: A Review of the Stated Frequencies of "Spread" After Thoracoplasty.

Anaesthesia	No. of Cases	No. of Operations	No. of Spreads	Frequency of Spread Pct. per Patient	Frequency of Spread Pct. per Operation
Adams and Dufault[11]	241	605	12	4.9	2.0
Schaffner and Found[12]	—	335	10	—	2.9
Harrison and Berry[13]	150	430	16	10.7	4.0
Parke et al.[9]	367	805	81	22	10.0
Kinsella et al.[1]	613	1574	90	14.7	5.34
Murphy et al.[14]	316	857	28	8.9	3.1
Murphy[3]					
Without Streptomycin	249	648	36	14.4	5.6
Streptomycin Umbrella	258	699	14	5.4	2.0
Yang and Lees[10]	317	1388	34	10.7	2.5

Results

(a) *Mortality:*

Of all the criteria of success of any operation the mortality afterwards is the only figure about which there is no dubiety. There can be no argument as to whether or not death has occurred within a fixed period after operation.

The entire mortality of this series was one case and that patient died of tuberculous bronchopneumonia in the days before streptomycin was available. There was no other death from any cause among these patients within two months of operation. Table IV gives the mortality figures in the recent English series and a few results from other sources are included.

It will be seen that the results obtained in the present series compare favorably indeed with those reported by other workers.

(b) *Spread Rate:*

The other yardstick by which the cost for anaesthesia for thoracoplasty may be measured is the frequency of subsequent spread of the disease. Spread, unlike mortality, is not a complication about whose occurrence there can be no doubt. Some authors think only of a rapidly developing bronchopneumonic tuberculous infection as "spread." Others also mention the development of tuberculosis in an area of lung which has become atelectatic after operation. Complications of these types have been classed in this essay as serious spreads and comparative statistics for their occurrence are given in Table V where there will be found the frequency of these accidents in the author's and in McHale's[2] and Millar's[4] cases. On this basis it is apparent that the use of general anaesthesia in no way adds to the incidence of such complications.

These disturbances are, however, not the only types of extension of tuberculosis of the lungs which may follow thoracoplasty. Quite often a patient weathers the first week or two after the operation without incident. Then some area of the lung which had previously had in it an area of healed tuberculous infection begins to become active again and the disease there progresses. It is the opinion of Price, Thomas and Cleland[6] that these complications are in no way related to the anaesthetic but it is difficult to say where a true bronchopneumonic spread has occurred and where a previously healed area has again become the seat of active disease. For

TABLE IX: The Frequency of Spread with Older Methods of Anaesthesia and with Nitrous Oxide, Oxygen and Curare.

Anaesthesia	No. of Cases	No. of Operations	No. of Spreads	Frequency of Spread Pct. per Patient	Frequency of Spread Pct. per Operation
Nitrous Oxide, Oxygen and Curare	126	259	12	9.5	4.6
Other Methods (Pilot Series)	—	112	11	—	10

this reason the author regarded as "spread" all cases where a radiological extension of the disease has been seen within two months of the operation. Similar criteria were employed by Parke, Loftus and Bishop[9] and by Yang and Lees[10] though the latter authors do not seem to have laid down any time limit and some of their cases must inevitably be instances of failure of the operation to control the disease with its inevitable spread to other areas of the lung. With these facts in view a list of all types of "spread" which have been noted in this series is set out in Table VI while in Table VII will be found the comparative results of the author and of the other workers using similar criteria. Again it will be seen that the incidence of spread in this series is by no means excessive. In Table VIII will be found the "spread" rate given by some other workers in this field but it must be emphasized that before figures are comparable, the same criteria of spread must be employed and the same operative procedures must be performed on patients with disease of approximately the same severity and extent. The significance of any differences in the figures is therefore not great and the only point of real interest is Murphy's[3] observation that streptomycin reduces but by no means abolishes the risk of the development of spread.

One additional comparison requires to be made. In Table IX will be found the spread rates in the pilot series and in the main group of cases. It is clear from these figures that not only, as has already been shown, is nitrous oxide and oxygen with curare at least as satisfactory a method as local anaesthesia. Its employment also makes the operation of thoracoplasty many times safer than it was with the older methods of general anaesthesia.

Comment

The facts here set out speak for themselves and discussion of them hardly seems necessary. It is obvious from what has been said in the body of this essay that properly conducted general anaesthesia does not increase and in fact may even decrease the mortality and spread rate after thoracoplasty. It must be emphasized, however, that the cases reported here occurred in the practice of a single specialist anaesthetist already skilled in the methods used in thoracic surgery. This essay, therefore, though a plea for the use of general rather than local anaesthesia for thoracoplasty is even more the case for the utilization of the services of a specialist anaesthetist in such cases if the greatest possible comfort is to be afforded to the patient with the minimal risk and maximally good operating conditions for the surgeon.

SUMMARY

The various types of anaesthesia for thoracoplasty are discussed. The advantages and drawbacks of local anaesthesia are considered, and it is concluded that the only justification for its use is a decrease in post-operative mortality and spread rate. A pilot investigation of the various anaesthetic techniques available for thoracoplasty was performed. General

anaesthesia with nitrous oxide and oxygen and curare seemed most satisfactory. A large series of cases were anaesthetized with this technique. The mortality in this group was gratifyingly low and the spread rate was by no means excessive. It is concluded that where the services of a skilled specialist anaesthetist are available there is no advantage in performing thoracoplasty under local anaesthesia.

RESUMEN

Se discuten los diferentes tipos de anestesia para la toracoplastía. Se consideran las ventajas y desventajas de la anestesia local y se concluye que la única justificación para su empleo es la disminución de la mortalidad postoperatoria y de la incidencia de propagaciones de la enfermedad. Se llevó a cabo una investigación piloto de las varias técnicas de anestesia disponibles para la toracoplastía. Parece que la anestesia general con óxido nitroso y oxígeno y curare es la más satisfactoria. Se empleó esta técnica de anestesia en una serie grande de casos. En este grupo la mortalidad fue bastante baja y la frecuencia de las propagaciones no fue elevada. Se concluye que cuando se cuenta con los servicios de un especialista adiestrado en la anestesia, no es ventajoso hacer toracoplastías bajo la anestesia local.

RESUME

L'auteur met en discussion les différentes méthodes d'anesthésie pour thoracoplastie. Il étudie les avantages et les inconvénients de l'anesthésie locale et sa conclusion est que la seule justification de son emploi est une dimiuntion de la mortalité et des ensemencements post-opératoires. Il a fait des essais de différentes techniques anesthésiques utilisables pour la thoracoplastie. Il lui semble que l'anesthésie au protoxyde d'azote, avec oxygène et curare est la plus satisfaisante. Un grand nombre de cas ont été anesthésiés par cette technique. Dans cet ensemble la mortalité fut extrêmement basse, et les ensemencements post-opératoires n'eurent rien d'excessif. Il conclut que lorsqu'on peut faire appel à un anesthésiste compétent, il n'y a pas avantage à utiliser l'anesthésie locale pour la thoracoplastie.

REFERENCES

1 Kinsella, T. J., Mariette, E. S., Matell, P. M., Fenger, E. P. K., Funk, V. K., Larson, L. M., Cohen, S. S. and Nemec, F. C.: "Thoracoplasty in the Treatment of Pulmonary Tuberculosis. An Analysis of Results Five to Twenty-Six Years After Operation," *Am. Rev. Tuberc.*, 59:113, 1949.

2 McHale, S. J.: "Some Considerations in the Post-operative Course of Patients Submitted to Thoracoplasty," *Brit. J. Tuberc.*, 43:99, 1949.

3 Murphy, J. S.: "Streptomycin in the Surgery of Pulmonary Tuberculosis," *Surg., Gynec. and Obst.*, 87:546, 1948.

4 Millar, E. J.: "Anaesthesia for Major Surgery in Thoracic Tuberculosis," *Tubercle*, 29:121, 1948.

5 Holmes Sellors, T.: "The Results of Thoracoplasty in Pulmonary Tuberculosis," *Thorax*, 2:216, 1947.

6 Price Thomas, C. and Cleland, W. P.: "Results of Thoracoplasty," *Brit. J. Tuberc.*, 37:2, 1943.

7 Hagn-Meincke, F.: "Late Results in Four Hundred Twenty Tuberculous Patients Subjected to Thoracoplasty," *J. Thoracic Surg.*, 19:837, 1950.

8 Gilbert, R. G. B.: "Anaesthesia in Pulmonary Tuberculosis," *Curr. Res. Anaes. and Analg.*, 28:219, 1949.

9 Parke, W. M., Loftus, E. R. and Bishop, H. F.: "The Effect of Anaesthesia and Surgery Upon Patients with Pulmonary Tuberculosis," *N. Y. State J. Med.*, 48: 1685, 1948.

10 Yang, S. C. H. and Lees, W. M.: "Spread or Exacerbation of Pulmonary Tuberculous Lesions as a Result of Thoracoplasty," *Am. Rev. Tuberc.*, 61:648, 1950.

11 Adams, R. and Dufault, P.: "Surgery in Pulmonary Tuberculosis," *J. Thoracic Surg.*, 11:43, 1941.

12 Schaffner, V. D. and Found, E. M.: "Spinal Anaesthesia in Thoracoplasty," *J. Thoracic Surg.*, 12:190, 1942.

13 Harrison, A. W. and Berry, F. B.: "Analysis of 150 Cases of Thoracoplasty for Tuberculosis at Bellevue Hospital," *J. Thoracic Surg.*, 12:292, 1943.

14 Murphy, J. D., Walkup, H. E. and Cheek, J. M.: "An Evaluation of Streptomycin as a Protective Agent Against Spreads, Reactivations and Wound Infections Following Thoracoplasty for Pulmonary Tuberculosis," *Surg. Clin. N. America*, (Philadelphia Number), p. 1555, 1948.

Association of Bronchogenic Carcinoma and Active Pulmonary Tuberculosis*

With Report of Four Cases

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History

Coexistent bronchogenic carcinoma and active pulmonary tuberculosis has been the source of considerable clinical and pathological interest and speculation for many years. Bayle[1] has usually been credited with the first reported case of simultaneous pulmonary cancer and tuberculosis,[2-4] although Fried[5,6] doubted the authenticity of this report. Fried preferred to consider Penard's[7] the first reliable report of the combination.

Question of Antagonism

The dictum of Rokitansky,[8] that tuberculosis and cancer in general were antagonistic, has been widely referred to.[9-14] Rokitansky theorized that when tuberculosis was present, cancer would not develop. Broders[10] doubted that such antagonism existed. Pearl[14] studied this problem with a statistical evaluation of autopsies. Pearl agreed with Rokitansky that an incompatability or antagonism existed between cancer and tuberculosis. Pearl found active tuberculosis in 6.6 per cent of patients dying of malignancy, and in 16.3 per cent of patients dying without malignant growths. Conversely, Pearl found malignancy in 1.2 per cent of 886 patients with active tuberculosis, and in 9.3 per cent of 886 patients without active tuberculosis. The latter group were of similar sex and age.

Carlson and Bell[15] made a similar study with comparable results, but they concluded that Pearl's reasoning was fallacious. They, too, found fewer cases of active tuberculosis in the group of patients who died of malignancy, than in the non-malignant group. However, they also found fewer cases of tuberculosis in the group with heart disease when compared to the group without. Carlson and Bell concluded that there was no support for the theory of antagonism. They felt that the statistical results could be attributed to the fact that the majority of the patients dying of tuberculosis had no other major disease.

Bronchogenic Carcinoma and Tuberculosis

Although there had been scattered reports of coexistent bronchogenic carcinoma and active pulmonary tuberculosis, it was not until 1935 that Fried[5] published his large series. Fried reported 13 cases of the combination proved by autopsy. Gerstl and co-workers[16] reported nine cases of the combined diseases. They included autopsy findings in four of those cases.

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Robbins and Silverman[4] found 11 cases of bronchogenic carcinoma and active pulmonary tuberculosis in a series of 6,500 autopsies.

Bronchogenic Carcinoma in Tuberculosis

The frequency of occurrence of bronchogenic carcinoma in cases of active tuberculosis has been reported by several authors. In the series by Robbins and Silverman, six of the 11 cases came from a tuberculosis sanatorium. There had been 400 autopsies at the sanatorium, so that six of the 400 tuberculous patients had bronchogenic carcinoma (1.5 per cent). De la Fuente and Palacios[17] found bronchogenic carcinoma in 35 of 2,500 autopsies of tuberculous patients in the Sea View Hospital (1.4 per cent).

Active Tuberculosis in Bronchogenic Carcinoma

Some early writers reported rather large numbers of patients with bronchogenic carcinoma showing active pulmonary tuberculosis. Many believed tuberculosis to be an etiological factor in the production of bronchogenic carcinoma. Wolf's series[18] has been widely quoted (131,113,6). Wolf collected 31 cases of malignancy of the lung, 13 of which had tuberculosis (41.9 per cent). Shaw[2] later analyzed Wolf's cases and concluded that at least five of the 13 were not authentic. Seafarth[19] reported that 15 per

TABLE I: Reported Incidence of Active Pulmonary Tuberculosis in Autopsied Cases of Bronchogenic Carcinoma.

Year Reported	Author	Tuberculosis	Bronchogenic Carcinoma
1924	Klotz[21]	2	24
1926	Grove and Kramer[22]	1	21
1929	Simpson[23]	6	139
1930	Davidson[24]	7	107
1933	Hruby and Sweany[25]	3	12
1935	Olson[26]	1	69
1935	Leader[27]	1	29
1935	Jaffe[28]	7	100
1936	Kramer and Som[29]	4	100
1938	Arkin[30]	4	85
1938	Bauer[31]	2	32
1938	Koletsky[32]	2	100
1938	Stein and Joslin[33]	4	100
1942	Perrone and Levinson[34]	1	38
1948	Fried[6]	34	319
1950	Reingold, Ottoman and Konwaler[35]	6	60
	TOTAL	85	1,335 (6.4%)

cent of 307 autopsied cases of cancer of the lung showed some form of tuberculosis.

Drymalski and Sweany[20] found acid-fast bacilli in the sputum of 15 of 57 cases of bronchogenic carcinoma (26 per cent). However, at autopsy seven of the 15 showed no sign of pulmonary tuberculosis.

In Table I is tabulated a review of the literature which revealed 85 cases of active pulmonary tuberculosis in 1,335 autopsied patients with bronchogenic carcinoma (6.4 per cent). Many series were excluded because no mention was made of the activity of associated pulmonary tuberculosis, or because the group reported was derived from clinical rather than postmortem material. In clinical series such as those diagnosed by bronchoscopic examination, tuberculosis could not be completely excluded.

Explanation of Associated Diseases

Various explanations have been given for the association of active pulmonary tuberculosis with bronchogenic carcinoma. Although tuberculosis was once considered an etiological factor in the development of bronchogenic carcinoma, recent authors have discredited this belief. Arkin[30] and Vinson[36] doubted that tuberculosis was a factor in the production of cancer of the lung.

Fried[5] presented a logical discussion as to the association of these diseases. He stated that pulmonary tuberculosis and bronchogenic carcinoma could coexist accidentally, or that one may be a factor in the causation of the other. Following this reasoning, three explanations are tenable:

1) The diseases are associated coincidentally.
2) Tuberculosis is a factor in the production of bronchogenic carcinoma.
3) Bronchogenic carcinoma activates a pre-existing pulmonary tuberculosis.

Many authors believe that the combination of the two diseases is a coincidental relationship. Hoffman,[37] in his study in 1929, was unable to establish any etiological connection between lung carcinoma and tuberculosis. Lemon and co-workers,[38] Olson,[26] and Stein and Joslin[33] thought the association of the diseases was a coincidence. Koletsky[32] found two cases of active tuberculosis in 100 autopsied bronchogenic carcinomas and thought the incidence of tuberculosis comparable to a control group.

Early writers found that a great proportion of the cases of bronchogenic carcinoma had what was considered active tuberculosis. They felt that tuberculosis predisposed to bronchogenic carcinoma. Some of these early cases were poorly documented. It is now known that in many instances bronchogenic carcinoma produces bronchial stenosis and associated nontuberculous cavitation. Such lesions could have readily been considered tuberculous before adequate bacteriology was established. A larger proportion of active tuberculosis was undoubtedly present in the general population in the 19th century than is present now. This, too, would account for more tuberculosis in the earlier series of bronchogenic carcinoma. Nevertheless, Ewing[39] felt in 1928 that tuberculosis was the chief etiological factor in the causation of cancer of the lung. Later, in 1940, he stated that

although tuberculosis was once the chief etiological factor in bronchogenic carcinoma, it was of diminishing importance.[40] Barron[41] also felt that tuberculosis was the chief etiological factor in the pathogenesis of carcinoma of the lung. Cases of bronchogenic carcinoma arising from tuberculous cavities have been described, and have been referred to in recent years.[38,27,3,20] Holman and Duff[42] thought that occasionally carcinoma resulted from metaplasia in chronic tuberculous cavitation.

Bronchogenic carcinoma is believed by some to activate pre-existing tuberculosis. Jaffe[28] came to this conclusion in his review of 100 autopsies of primary carcinoma of the lung. He found seven cases of active pulmonary tuberculosis which he thought could have been activated by the coexisting malignancy.

Method and Materials

A review of the autopsy records at Ancker Hospital, St. Paul, Minnesota, revealed 96 cases of bronchogenic carcinoma in the 25 years from 1926 through 1950. There were 12,055 autopsies during that period. Ninety of the patients were white and six were Negro. Seventy-three were male and 23 were female. Their ages ranged from 27 to 82 years with a median of 62 years.

In the same 25 year period there were 1,177 instances of pulmonary tuberculosis. Of these, 415 were considered inactive while 726 were active (Table II).

Four patients were found to have coexistent bronchogenic carcinoma and active pulmonary tuberculosis. This group comprised 4.2 per cent of the total with bronchogenic carcinoma and 0.6 per cent of those with active pulmonary tuberculosis. These four patients were white males. Their ages ranged from 35 to 76 years. The following is a synopsis of each case:

CASE 1.

History: H.F. (191595) was a 76 year old single, white male who entered Ancker Hospital on March 13, 1929, with the complaints of weakness, constipation, loss of weight, and epigastric distress. He had noted abdominal distress for 10 years with a sudden exacerbation four months before admission. Three months before admission he developed a cough and raised considerable sputum.

Physical examination: He was markedly emaciated. The chest was of the funnel type. Lung fields were clear. The rest of the examination was non-contributory.

Laboratory: Hemoglobin varied from 68 to 83 per cent. White blood count was normal. Urinalysis and Wassermann were negative. Three thorocenteses revealed

TABLE II: Pulmonary Tuberculosis in 12,055 Autopsies from 1926 through 1950.

INACTIVE (apical scarring, primary complex, etc.)		415
ACTIVE		762
Caseating	129	
Cavitating	601	
Miliary	32	
	TOTAL	1,177

reddish-brown fluid with a specific gravity of 1.020. There was no growth on culture.

X-ray: Upper and lower gastro-intestinal series were negative. Chest x-ray film demonstrated a large, fairly localized shadow extending from the right border of the heart to the base of the lung. There was probable atelectasis of the right lower lobe and fluid in the right pleural cavity on later chest films.

Course: The patient soon had right chest pain and raised considerable blood-streaked sputum. He developed signs of pleural effusion which was removed by pleural tap. He had marked anorexia, became progressively weaker, and died on May 21, 1929, three months after admission.

Autopsy: There were 600 cc. of slightly bloody fluid in the right pleural cavity. The right lung was almost entirely collapsed. There was a tumor which replaced most of the right lower lobe. In the apex of the right lower lobe were found multiple abscesses which were rather caseous in character. The abscess walls were soft and necrotic. There were several large tumor nodules on section of the liver. The heart showed coronary sclerosis. The gastro-intestinal tract was negative.

Microscopic section: The lung showed multiple tubercles with central necrosis and surrounding epithelioid cells and Langhan's giant cells. In the same section were epithelial cells with dark-staining nuclei arranged in a scattered fashion or as indefinite glands. Frequent mitoses were seen.

Diagnosis: 1) Bronchogenic carcinoma, right (alveolar cell).
2) Active pulmonary tuberculosis, right.

CASE 2.

History: W.C. (A66674) was a 35 year old man who entered Ancker Hospital on February 23, 1936, with a productive cough, hemoptosis, weight loss, and chest pain. He had been seen elsewhere in December 1930, with similar complaints. X-ray film inspection in 1930 revealed a right hilar mass and bronchoscopy, a fungating mass in the right lower lobe bronchus which on biopsy proved to be carcinoma. During the first portion of 1931, deep x-ray therapy was given. Al-

TABLE III: Clinical Summary of Four Cases of Coexistent Bronchogenic Carcinoma and Active Pulmonary Tuberculosis.

	Case 1	Case 2	Case 3	Case 4
Age	76 years	35 years	51 years	57 years
Sex	Male	Male	Male	Male
Race	White	White	White	White
Duration of symptoms	6 months	6 years	2 months	6 months
Cough	Yes	Yes	Yes	Yes
Sputum	Moderate	Marked	Moderate	Minimal
Hemoptosis	Yes	Yes	Yes	No
Fever, degrees Fahrenheit	None	To 103	To 103	None
Chest pain	Yes	Yes	Yes	Yes
Sputum for acid-fast bacilli	Not examined	Negative	Positive	Negative
Clinical diagnosis	Cancer of the lung?	Bronchogenic carcinoma	Tuberculosis	Bronchogenic carcinoma and tuberculosis

though there was temporary improvement, the symptoms recurred and progressed in severity.

Physical examination: The patient was a well developed, fairly well nourished, white male who appeared listless. There was pigmentation of the skin of the chest in the area of the x-ray therapy. There was decreased expansion of the right chest with dullness over the lower two thirds. Many fine rales were heard above the dullness on the right.

Laboratory: Hemoglobin was 80 per cent, and the white count was 35,200 with 91 per cent pmn's. Sedimentation rate was 46 mm. Seven sputum specimens were negative for acid-fast bacilli.

X-ray: Chest x-ray film showed an increased density in the right chest with no shift in the mediastinum.

Course: He raised large amounts of purulant sputum, had noticeable respiratory distress, became weaker, and expired on April 3, 1936.

Autopsy: There were pleural adhesions on the left with 75 cc. of blood-tinged fluid. The right lung was also adherant and 200 cc. of foul-smelling pus was present in the pleural cavity. Section of the right lung showed numerous small communicating cavities filled with white purulant material in the apex of the lower lobe. The bronchus to this area was occluded by a papillomatous tumor about 1 cm. in diameter. In the left lung were scattered areas of consolidation which, in some areas, were confluent.

Microscopic section: The bronchial tumor consisted of nests of epithelial cells with darkly-staining nuclei and scanty cytoplasm, growing aberrantly, but with a tendency to glandular formation. Sections of the right lung through the area of cavitation showed the normal structure to be entirely obliterated by an overgrowth of connective tissue and epithelioid cells. Occasional giant cells were seen. There was necrotic tissue with acute and chronic inflammatory cells in the walls of the cavity. Sections of the left lung were non-contributory.

Diagnosis: 1) Bronchogenic carcinoma, right (small cell).
2) Active pulmonary tuberculosis, right.
3) Bronchopneumonia.
4) Empyema, right.

CASE 3.

History: E.A. (A91344) was a 51 year old, white male who entered the hospital May 10, 1938. He had worked regularly as a butcher until six weeks before admission when he had a sudden onset of pleurisy on the right. He noticed an elevated temperature and a productive cough. He had anorexia, weakness, and a 35 pound

TABLE IV: Pathological Summary of Four Cases of Coexistent Bronchogenic Carcinoma and Active Pulmonary Tuberculosis.

	Case 1	Case 2	Case 3	Case 4
Tumor type	Alveolar cell	Small cell	Squamous cell	Squamous cell
Tumor location	Right lower lobe	Right lower lobe	Right hilus	Right upper lobe
Tuberculosis location	Right lower lobe	Apex right lower lobe	Right lower lobe	Right upper lobe
Extrapulmonary metastases	Liver	Mediastinum	Mediastinum pericardium, and heart	None
Extrapulmonary tuberculosis	None	None	None	None

weight loss. After three weeks, his sputum became blood-tinged, and he soon developed dyspnea on exertion.

Physical examination: The patient was found to be an emaciated male who was coughing and raising sputum. Temperature was 100 degrees F. and pulse was 110. There was dullness over the entire right chest, with coarse rales in the upper lung field. Bronchovesicular breathing was heard over the right chest, except for the lower field where breath sounds were diminished. Bilateral inguinal hernia was present.

Laboratory: Hemoglobin was 66 per cent. White blood count was 10,000 with 68 per cent pmn's. Sedimentation rate was 80 mm. per hour. Three sputum specimens were positive for acid-fast bacilli.

X-ray: An x-ray film showed extensive infiltration throughout the right lung. Heart and mediastinum were moderately displaced to the right. A density in the right base was considered to represent hydrothorax or a large cavity.

Course: The patient became progressively weaker and expired on his 11th hospital day shortly after an hemoptosis of five ounces of bright-red blood.

Autopsy: There was obliteration of the right pleural cavity. The right lung weighed 880 grams and at the hilus there was a large firm tumor mass, 10 by 5 cm., which extended through the pericardium to the right auricle. There was calcification of the right hilar nodes. A large irregular cavity, 8 by 9.5 cm., was present in the right lower lobe. The lining of the cavity was ragged and necrotic and apparently consisted of tumor tissue in certain areas. There was a large branch of the pulmonary artery protruding into the cavity. The rest of the right lower lobe was semi-necrotic, but tuberculous tissue was not recognized grossly. The left lung weighed 435 grams and was negative on section.

Microscopic section: The lung showed definite areas of caseation surrounded by Langhan's giant cells and lymphocytes. The tumor consisted of epithelial cells in clusters and irregular glands.

Diagnosis: 1) Bronchogenic carcinoma, right (squamous cell).
2) Active pulmonary tuberculosis, right.

CASE 4.

History: A.M. (A145945) was a 57 year old, married, white male, admitted to Ancker Hospital on December 30, 1946, because of dyspnea, orthopnea, and right chest pain. He had noticed a chronic cough for 10 years. Six months before, he had been treated elsewhere for right upper lobe pneumonia which failed to resolve completely. Hydrothorax developed and repeated thorocenteses were made. Examination of the fluid revealed acid-fast bacilli and apparently, on one occasion, tumor cells. Thoracotomy was done and demonstrated a tumor mass which proved to be carcinoma on histological examination. Shortness of breath and chest pain developed. Prior to admission, swelling of the face, hands, and feet appeared.

Physical examination: Examination revealed a well nourished, afebrile man who had dyspnea and orthopnea. He had a surgical scar on the right chest which was well healed. Poor expansion of the right chest was noted. There was dullness on the right with absent breath sounds posteriorly and bronchial breathing anteriorly. The abdomen was distended with fluid. There was pitting edema of the face, hands, feet, and lower legs. Venous distention was observed.

Laboratory: Hemoglobin was 10 grams and white count was 18,050 with 88 per cent pmn's. Sedimentation rate was 58 mm. per hour. Sputum on one occasion was negative for acid-fast bacilli.

X-ray: Chest x-ray film inspection revealed a homogeneous density in the right hemithorax. Several small densities were noted in the left upper lung field peripherally.

Course: The patient had progressive dyspnea and soon became disoriented. On January 4, 1947, five days after admission, he expired.

Autopsy: There were 300 cc. of serous fluid in the left pleural cavity, and 1,500 cc.

in the right. There was a tumor thrombus in the right pulmonary vein. The right lung weighed 1,000 grams and a large tumor extended from the hilus to the right upper lobe. There was tumor in the right main bronchus. The right upper lobe revealed areas of cavitation filled with thick yellow purulant material. The tumor mass in the right lung was firmly adherent to the mediastinal structures including the arch of the aorta. The left lung weighed 573 grams, and there were small scattered tumor nodules in the upper lobe.

Microscopic section: The lung revealed aberrantly growing sheets of epithelial cells. Occasional mitotic figures were seen. Intimately associated with the tumor were areas of caseation with typical tubercles.

Diagnosis: 1) Bronchogenic carcinoma, right (squamous cell).
2) Active pulmonary tuberculosis, right.

It may be noted that in every instance the carcinoma and tuberculosis were in close proximity. The clinical diagnosis in two cases was bronchogenic carcinoma; in another, combined bronchogenic carcinoma and tuberculosis; and in the fourth, tuberculosis. In one patient acid-fast bacilli and malignant cells were found in the pleural fluid; in another, acid-fast bacilli were present in the sputum; the diagnosis of carcinoma was established by biopsy during bronchoscopic examination for another, and in the last case neither diagnosis was established before death. Table III reviews the clinical findings in the four patients, while Table IV reviews the pathological findings.

Discussion

The close association of bronchogenic carcinoma and active pulmonary tuberculosis in the four cases reported would be unusual in a chance relationship. It seems likely that one may be an etiological factor in the production of the other. Pulmonary tuberculosis is usually a peripheral lesion while bronchogenic carcinoma is usually a central one. If pulmonary tuberculosis were a factor in producing cancer of the lung, more peripheral malignancies would be expected. On the other hand, centrally located bronchogenic carcinoma could readily cause a breakdown of a pre-existing peripheral pulmonary tuberculosis, because of the altered circulation and bronchial stenosis which is associated with this malignancy.

The author wishes to thank Dr. John F. Noble for making available the autopsy records of Ancker Hospital, and for helpful suggestions during preparation of this paper.

SUMMARY

The history of coexistant bronchogenic carcinoma and active pulmonary tuberculosis has been reviewed.

The literature reveals that bronchogenic carcinoma occurred in 1.4 per cent of autopsied cases of active pulmonary tuberculosis. Conversely, active pulmonary tuberculosis occurred in 6.4 per cent of the bronchogenic carcinomas in a review of recent autopsy series.

Four autopsied cases of coexistent bronchogenic carcinoma and active pulmonary tuberculosis have been reported. There were 726 cases of active pulmonary tuberculosis in the past 25 years, so the incidence of bronchogenic carcinoma was 0.6 per cent in this group. In the same period 96 bronchogenic carcinomas were autopsied, so that 4.2 per cent of these patients had associated active pulmonary tuberculosis.

Although the associated diseases may occur coincidentally, at times bronchogenic carcinoma may activate pre-existing pulmonary tuberculosis.

RESUMEN

Ha sido revisada la historia del carcinoma broncogénico coexistente con la tuberculosis pulmonar activa coexistente.

La bibliografía revela que el carcinoma broncogénico ocurre en el 1.4 por ciento de casos autopsiados de tuberculosis pulmonar activa, e inversamente, la tuberculosis pulmonar activa se presentó en el 6.4 por ciento de los carcinomas broncogénicos, en la revisión de una serie reciente de autopsias.

Han sido referidos cuatro casos autopsiados de carcinoma broncogénico y tuberculosis pulmonar coexistente. Hubo 726 casos de tuberculosis pulmonar activa en los últimos 25 años, así que la frecuencia del carcinoma broncogénico fué de 0.6 por ciento en éste grupo. En el mismo periodo, 96 carcinomas broncogénicos fueron autopsiados, resultando que un 4.2 por ciento de esos casos tenían tuberculosis pulmonar activa asociada.

Aunque estos padecimientos asociados pueden presentarse coexistentes, en algunas ocasiones el carcinoma broncogénico puede activar la tuberculosis pulmonar pre-existente.

RESUME

L'auteur fait un exposé de l'histoire de la coexistence de cancer bronchique et de tuberculose pulmonaire active.

La littérature révèle que l'on peut constater un cancer bronchique dans 4% des cas de tuberculose pulmonaire active qui ont été autopsiés. Inversement, dans une étude de plusieurs séries récentes d'autopsies de tuberculose pulmonaire active, apparurent dans 6.4% des cancers bronchiques.

L'auteur rapporte quatre cas avec autopsie où coexistaient un cancer bronchique et une tuberculose pulmonaire active. Dans 726 observations de tuberculose pulmonaire active vues dans les dernières vingt-cinq années, il y eut 0.6% de cancers bronchiques. Dans la même période, on fit l'autopsie de 96 cancers bronchiques et dans 4.2% de ces malades, il y avait une tuberculose pulmonaire active associée.

Bien qu'on ne puisse exclure complètement la coïncidence, il semble que le cancer bronchique donne un coup de fouet à la tuberculose pulmonaire pré-existante.

REFERENCES

1 Bayle, G. H.: "Recherches sur la phtisie pulmonaire," Paris: Gabon, 1810, p. 310.
2 Shaw, H. B.: "Case of Malignant Disease of the Lung with Pseudo-Tuberculosis," *Brit. M. J.*, 1:1331, 1901.
3 Simons, E. J.: "Primary Carcinoma of the Lung," Chicago: The Year Book Publishers, Inc., 1937.
4 Robbins, E. and Silverman, G.: "Coexistent Bronchogenic Carcinoma and Active Pulmonary Tuberculosis," *Cancer*, 2:65, 1949.
5 Fried, B. M.: "Bronchiogenic Cancer Combined with Tuberculosis of the Lungs," *Am. J. Cancer*, 23:247, 1935.
6 Fried, B. M.: "Bronchiogenic Carcinoma and Adenoma," Baltimore: Williams and Wilkins Co., 1948, pp. 59-63.
7 Penard, M.: "Cancer et tubercule du poumon," *Bull. Soc. Anat. de Paris*, 21: 260, 1846.
8 Rokitansky, C.: "A Manuel of Pathological Anatomy," Philadelphia: Blanchard and Lea, 1855, Vol. 1, pp. 237-238.
9 Adler, I.: "Primary Malignant Growths of the Lungs and Bronchi: A Patho-

logical and Clinical Study," New York: Longmans, Green and Co., 1912, p. 33.
10 Broders, A. C.: "Tuberculosis Associated with Malignant Neoplasia," *J.A.M.A.*, 72:390, 1919.
11 Fried, B. M.: "Primary Carcinoma of the Lung," *Medicine*, 10:373, 1931.
12 Cooper, F. G.: "The Association of Tuberculosis and Carcinoma," *Am. Rev. Tuberc.*, 25:108, 1932.
13 Fishberg, M.: "Pulmonary Tuberculosis," Philadelphia: Lea and Febiger, 1932, Vol. 2, pp. 225-227.
14 Pearl, R.: "Cancer and Tuberculosis," *Am. J. Hyg.*, 9:97, 1929.
15 Carlson, H. A. and Bell, E. T.: "A Statistical Study of the Occurrence of Cancer and Tuberculosis in 11,195 Postmortem Examinations," *J. Cancer Research*, 13: 126, 1929.
16 Gerstl, B., Warring, F. C. and Howlett, K. S.: "Cancer and Pulmonary Tuberculosis; Diagnostic Problems in Patients with Cancer of the Lung in the Presence of Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 54:470, 1946.
17 Fuente, M. A. de la, and Palacios, H. R.: "Undifferentiated Cell Carcinoma of the Lung and Chronic Pulmonary Tuberculosis; Case Report," *Quart. Bull., Sea View Hosp.*, 7:314, 1942.
18 Wolf, K.: "Der primare Lungenkrebs," *Fortschr. d. Med.*, 13:725, 1895.
19 Seyfarth, C.: "Lungenkarzinome in Leipzig," *Deutsche med. Wchnschr.*, 50:1497, 1924.
20 Drymalski, G. W. and Sweany, H. C.: "The Significance of Pulmonary Tuberculosis when Associated with Bronchogenic Carcinoma," *Am. Rev. Tuberc.*, 58:203, 1948.
21 Klotz, O.: "Cancer of the Lung; With a Report Upon Twenty-four Cases," *Canad. M. A. J.*, 17:989, 1927.
22 Grove, J. S. and Kramer, S. E.: "Primary Carcinoma of the Lung," *Am. J. M. Sc.*, 171:250, 1926.
23 Simpson, S. L.: "Primary Carcinoma of the Lung," *Quart. J. Med.*, 22:413, 1929.
24 Davidson, M.: "Cancer of the Lung and Other Intrathoracic Tumours," London: John Wright and Son, 1930, p. 39.
25 Hruby, A. J. and Sweany, H. C.: "Primary Carcinoma of the Lung, with Special Reference to Incidence, Early Diagnosis, and Treatment," *Arch. Int. Med.*, 52: 497, 1933.
26 Olson, K. B.: "Primary Carcinoma of the Lung; Pathological Study," *Am. J. Path.*, 11:449, 1935.
27 Leader, S. A.: "The Coexistence of Primary Carcinoma of the Lung and Pulmonary Tuberculosis with a Case Report," *M. Bull. Vet. Admin.*, 12:78, 1935.
28 Jaffe, R. H.: "Primary Carcinoma of the Lung; A Review of 100 Autopsies," *J. Lab. and Clin. Med.*, 20:1227, 1935.
29 Kramer, R. and Som, M. L.: "Bronchoscopic Study of Carcinoma of the Lung; An Analysis of 300 Cases of Bronchial Carcinoma with 100 Postmortem Examinations," *Arch. Otolaryng.*, 23:526, 1936.
30 Arkin, A.: "Primary Carcinoma of the Lung; A Clinical Study of 160 Cases in Five Years," *J. Kansas M. Soc.*, 39:369, 1938.
31 Bauer, J. T.: "A Review of the Primary Carcinomas of the Lungs and Pleurae Occurring in 6,000 Consecutive Necropsies," *Bull. Ayer Clin. Lab.*, Pennsylvania Hosp., 3:139, 1938.
32 Koletsky, S.: "Primary Carcinoma of the Lung; A Clinical and Pathological Study of 100 Cases," *Arch. Int. Med.*, 62:636, 1938.
33 Stein, J. J. and Joslin, H. L.: "Carcinoma of the Bronchus; A Clinical and Pathological Study of 164 Cases," *Surg., Gynec. and Obst.*, 66:902, 1938.
34 Perrone, J. A. and Levinson, J. P.: "Primary Carcinoma of the Lung (Report of 115 Cases, 38 Autopsies and 77 Bronchoscopic Biopsies)," *Ann. Int. Med.*, 17:12-25, July 1942.
35 Reingold, I. M., Ottoman, R. E. and Konwaler, B. E.: "Bronchogenic Carcinoma; A Study of 60 Necropsies," *Am. J. Clin. Path.*, 20:515, 1950.
36 Vinson, P. P.: "Primary Malignant Disease of the Tracheobronchial Tree; Report of 140 Cases," *J.A.M.A.*, 107:258, 1936.
37 Hoffman, F. L.: "Cancer of the Lungs," *Am. Rev. Tuberc.*, 19:392, 1929.
38 Lemon, W. S., Vinson, P. P., Moersch, H. J. and Kirklin, B. R.: "Primary Carcinoma of the Bronchus," *Southwestern Med.*, 16:485, 1932.
39 Ewing, J.: "Neoplastic Diseases," Philadelphia: W. B. Saunders Co., 1928, p. 852.
40 Ewing, J.: "Neoplastic Diseases," Philadelphia: W. B. Saunders Co., 1940, p. 873.
41 Barron, M.: "Carcinoma of the Lung: A Study of Its Incidence, Pathology, and Relative Importance," *Arch. Surg.*, 4:624, 1922.
42 Holman, W. L. and Duff, G. L.: "Primary Carcinoma of the Lung," *Am. J. M. Sc.*, 196:436, 1938.

American College of Chest Physicians

Report of the Committee on Chemotherapy and Antibiotics

This report is not intended as a detailed treatise on the chemotherapy of tuberculosis and nontuberculous chest diseases but rather as a progress report or statement on currently accepted principles and regimens to serve as a general guide to the physician treating tuberculosis and other chest diseases. Perhaps it is needless to mention that with respect to some problems encountered there is definite difference of opinion. When such is the case, it is so stated. Other questions are as yet unanswered but likely will be in the course of time.

In most tuberculosis hospitals in the United States today the use of streptomycin - PAS therapy has become substantially routine treatment for all patients with active and potentially progressive tuberculosis. Recommendations of previous years that streptomycin - PAS treatment be deferred in those cases where other therapeutic measures likely would be successful have now been modified in the interest of achieving more rapid and more durable therapeutic benefits. The marked trend toward long-term antimicrobial therapy has been noteworthy and this principle is now almost universally accepted.

Present Status of Streptomycin and PAS in the Treatment of Various Forms of Tuberculosis

Pulmonary Tuberculosis: The well established, generally accepted specific therapy for pulmonary tuberculosis at this time is intermittent combined use of streptomycin (or dihydrostreptomycin) 1 gm. intramuscularly two to three times weekly and NaPAS (the sodium salt of para-aminosalicylic acid) 12 to 15 gm. daily for prolonged periods. This regimen has proved to be very efficacious. Used in this manner the incidence of toxic phenomena (hearing loss with dihydrostreptomycin and vestibular disturbance with streptomycin) is lessened and the emergence of drug-resistant organisms can be greatly delayed. A minimum period of six to nine months is recommended, and many patients will benefit from much longer periods of 12 to 18 months or more, depending on the type of tuberculosis under treatment. Procedures such as pneumothorax and pneumoperitoneum when applicable should be induced relatively early during the period of chemotherapy. Thoracoplasty and resection should be done at the optimum time during treatment. In most cases surgical resection should be deferred until after six to nine months—though there is some difference of opinion on this point, depending in part on the type of disease present and its response to chemotherapy. Resection should be followed by three months or more of chemotherapy. Obviously, in a disease as variable and unpredictable as tuberculosis, the optimum time for surgical intervention can be determined only after careful clinical and laboratory evaluation of the case by the physician and the chest surgeon. It is emphasized again and again that chemotherapy is *not* a substitute for rest and other proven procedures in

the management of tuberculosis, but a very valuable adjunct and should be used as such.

Acute Miliary Tuberculosis: A combined daily regimen of streptomycin 1 gm. intramuscularly and oral NaPAS 15 gm. daily in three or four divided doses is indicated and is usually administered continuously for six months following remission as determined by symptomatology, chest roentgenograms, and bacteriologic examinations. Continuous, prolonged combined chemotherapy is to be stressed. If the patient does not tolerate oral NaPAS, parenteral PAS may be given, either intravenously or subcutaneously. Small quantities of hyaluronidase added to parenteral PAS aids in more rapid absorption when given subcutaneously.

Tuberculous Meningitis: During the early acute phase of the disease streptomycin intramuscularly 2 gm. daily and oral NaPAS 15 gm. or more daily is recommended. When the acute phase is over—usually after a few months—the dosage of streptomycin may be reduced to 1 gm. daily and the regimen continued for a year or more. Streptomycin sulfate or streptomycin calcium chloride is preferred to dihydrostreptomycin when higher daily doses are used for prolonged periods because the former is less likely to cause serious neurotoxic reactions than the latter. Until recently it has also been considered standard practice to use streptomycin intrathecally daily for several weeks, then every other day for several weeks more, in doses ranging from 50 to 100 mgm. per injection. However there is a growing conviction among a number of investigators that intrathecal streptomycin is not only unnecessary but may be undesirable on the ground that: (1) serious reactions and even deaths have been reported as a result of intrathecal streptomycin therapy, (2) spinal fluid drug levels are well above the reported in vitro bactericidal level required, (3) patients do not accept this treatment well over long periods, and (4) results in the treatment of meningitis in adults with and without intrathecal streptomycin appear to be comparable. Further research and study is necessary to resolve this problem, but there is reason to hope that intrathecal therapy will be found unnecessary as is the case in so many forms of nontuberculous meningitis. Reports on the intrathecal administration of tuberculin and fibrinolytic substances appear to be favorable but their role in therapy must await further investigations. Preliminary reports on results of the use of isoniazid in treatment of tuberculous meningitis, if confirmed by longer periods of observation, will undoubtedly modify the present therapeutic approach to this form of the disease.

Present Status of Isonicotinic Acid Hydrazide (Isoniazid)

There has been tremendous interest in this antituberculosis agent by physicians as well as the public since its dramatic—and unfortunately premature—announcement by the newspapers in February, 1952. It seems particularly important that its present status be critically evaluated at this time, based on the latest available studies by experienced investigators, and that a report be made to the members of the College and other interested physicians who may have occasion to treat tuberculosis.

General Considerations: Isoniazid, is an extremely potent antituberculosis agent, both in vitro and in vivo. It is bacteriostatic in vitro in concentrations as low as 0.05 mcg/ml. In experimental tuberculosis in animals it has proved equal or superior to streptomycin as a therapeutic agent. Its toxicity in man is relatively low in dosage ranges of 3 to 5 mg/kg body weight. Some of the more commonly occurring side reactions in this dosage range are constipation, hyperreflexia, positional hypotension and dizziness. Some workers are exceeding these dosages considerably and report no appreciable increase in toxic reactions except in elderly patients. Other investigators caution against the higher dosages because of the potential toxic effect on the central nervous system. Particularly in epileptics is caution urged; also in patients with pre-existing kidney dysfunction. Whether the higher doses are more effective therapeutically remains to be determined. Certainly at this time, the optimum dosage has not been established.

No serious disturbance of liver or kidney function has been reported as yet. In only an occasional patient are toxic side reactions sufficiently severe to necessitate discontinuing the drug. However in view of some reported instances in which serious complications have occurred during its administration, the committee emphasizes the need for vigilance and careful observation of patients receiving it.

Isoniazid administered orally is rapidly absorbed from the gastrointestinal tract, from one-half to three-fourths of the ingested dose being excreted by the kidney within 24 hours. It can also be given intravenously or intramuscularly if necessary. It permeates body tissues and fluids in effective concentration (which is especially important in tuberculous meningitis). It has a wide margin of safety with reference to therapeutic ratio. Drug resistant organisms are reported to emerge in a majority of cases after two to three months treatment with isoniazid alone. Though the relationship of the emergence of isoniazid-resistant organisms to the clinical picture is not as yet clearly defined, the committee feels that until conclusive evidence is found to the contrary, it must be assumed that the emergence of isoniazid resistance probably has the same ultimate clinical significance as has the emergence of streptomycin resistance. For the time being, until further careful studies yield the answer to this problem of drug resistance, the use of isoniazid *alone* is *not* recommended, except in investigational work. It is the opinion of the committee that isoniazid will probably find its greatest usefulness when administered in combination with streptomycin and PAS.

Though much remains to be learned about isoniazid, considerable information has been accumulated and the committee feels that certain tentative conclusions may be drawn at this time.

Isoniazid is not a miracle cure for tuberculosis and is not recommended as a substitute for such measures as bed rest, collapse procedures and appropriate surgery. It cannot be emphasized too strongly that tuberculosis requires planned, integrated treatment with rest, chemotherapy and surgical intervention when indicated.

Information obtained both from published reports and from communications from many experienced investigators in the United States and Europe indicate that—

In pulmonary tuberculosis use of isoniazid results in early symptomatic improvement, often dramatic with reduction in fever, cough and expectoration. The appetite improves and gain in weight occurs frequently. Some investigators report that roentgenographic improvement compares favorably, in similar types of lesions, with that obtained with streptomycin and PAS for similar periods. Other workers protest that isoniazid, though effective in producing x-ray improvement, is not the equal of streptomycin and PAS in this respect. Isoniazid has proved useful as an "umbrella" in resective surgery in patients whose organisms are streptomycin-resistant. Roentgenographic improvement in streptomycin-resistant cases has proved disappointing in a large majority of patients studied.

In tuberculosis of mucous membranes, e.g. tongue, laryngeal and tracheobronchial, the response to isoniazid is similar to that with streptomycin and PAS.

In tuberculosis of the genitourinary tract, serous membranes, glands, and in tuberculous sinus tracts, reports are too few and the studies of too short duration for adequate evaluation. However, in general, they tend to be favorable thus far.

Acute miliary tuberculosis reports to date indicate that results with isoniazid, in oral doses of 5 to 7 mgm/kg body weight daily are approximately equal to those obtained with streptomycin and PAS for similar periods. In one series of 12 patients treated for periods of three to nine months no relapses were reported. While such progress reports are most encouraging, other evidence suggests that this form of the disease may best be treated by combining daily streptomycin intramuscularly, NaPAS orally and isoniazid. The committee tends to favor this combined regimen until such time as further investigation yields the answer to this question. Treatment should be started early and continued for at least one year.

In tuberculous meningitis also, preliminary reports indicate that results with isoniazid alone in daily oral doses of 5 to 7 mgm/kg body weight are approximately equal to those obtained with streptomycin and PAS given for similar periods. Symptomatic improvement is rapid and dramatic, and spinal fluid cultures are usually negative for tubercle bacilli after the first month of treatment. The relapse rate among patients who survive for two months or more is thus far reported as slight, though this may increase with further observation. In view of such encouraging reports with the use of isoniazid alone, the committee believes for the time being at least, a regimen should be recommended which combines daily isoniazid orally, streptomycin intramuscularly and NaPAS continued for a year or more.

Treatment of Childhood Tuberculosis

The use of chemotherapeutic agents in the treatment of active primary tuberculosis is still rather controversial. Some believe that streptomycin

and PAS should be used in *all* cases proved to be active. However, it must be remembered that most cases run a benign course and by treating every such patient many workers feel that the efficacy of these drugs may be lost, due to the development of drug-resistant organisms, in the event that reinfection type tuberculosis develops later. Much remains to be learned regarding this question, but certain observations can be made that are consistent with current good practice. Careful supervision of the patient, including frequent chest x-rays should be maintained. When progression is noted by serial x-rays, when there is evidence that retrogression is not proceeding at a satisfactory rate, or when the patient is not doing well clinically, chemotherapy should be instituted without delay. Patients showing massive roentgen shadows of collapse due to a hilar node, the so-called "epituberculosis," should be treated. Every effort should be made toward re-expansion or resolution in these types to prevent the serious complication of bronchiectasis which so often ensues. Should bronchiectasis occur nevertheless, appropriate antibiotics are indicated to hold the secondary infection to a minimum. Moreover, all types of tuberculosis of bones and joints, of the genitourinary tract, and generalized lymphogenous tuberculosis when complicating the primary infections, should be treated immediately. Obviously all primary tuberculosis complicated by miliary or meningitic spread should be treated immediately and vigorously. Children usually tolerate streptomycin well and have few reactions. Treatment with streptomycin and PAS may be extended as long as a year. Isoniazid has not yet been used extensively enough in children for definite evaluation at this time.

Minimal Pulmonary Tuberculosis: Minimal active pulmonary tuberculosis, particularly of the exudative type, should receive early and prolonged chemotherapy with streptomycin and PAS for a minimum of six to nine months—perhaps longer. A proper rest regimen should be combined with chemotherapy for best results. Whether chemotherapy in such cases may be considered definitive or whether wedge resection should be combined with chemotherapy as recommended by some workers is still a much debated question at this time. Likewise the place of isoniazid in minimal tuberculosis remains to be evaluated.

Other Anti-Tuberculosis Agents

Cortisone and Tuberculosis: There is now general agreement that cortisone has no place in the treatment of tuberculosis. Because it can cause wide-spread dissemination of even apparently inactive tuberculosis, physicians are cautioned against its use for other diseases in patients with any evidence of tuberculosis. Even in the absence of known tuberculosis, chest x-rays should be taken before and several weeks after hormone treatment. If cortisone *must* be given for a very serious nontuberculous condition in a patient with tuberculosis, it should be combined with the use of streptomycin and PAS.

Other antituberculosis agents are mentioned briefly in the following paragraphs. However it appears clear that the development of isoniazid

has reduced the frequency with which these agents of marginal value need to be called upon.

T.B.I. (amithiozone) in doses of 100 mgm. daily has demonstrated definite but limited benefit in the treatment of patients with advanced pulmonary tuberculosis. Toxic and allergic reactions, including progressive anemia, granulocytopenia and toxic hepatitis, occur with sufficient frequency to limit its usefulness and necessitate frequent laboratory examinations. It is not as effective as PAS with streptomycin and its use should be limited to patients resistant to streptomycin and PAS or where streptomycin and PAS cannot be employed because of toxic or allergic reactions. Bacterial resistance to T.B.I. develops frequently following six months of treatment with 100 mgm. daily.

Viomycin is still under investigation and shows some promise but is not recommended for general use at this time because of toxic manifestations, such as allergic phenomen, renal irritations, vertigo and electrolyte changes.

Pyrazinamide is a drug that has shown early promise as an antituberculosis agent. The symptomatic response is similar to that of isoniazid but drug resistance occurs early, usually in six to eight weeks. For this reason its use is limited.

Terramycin when used in combination with streptomycin is reported to delay the emergence of drug resistant organisms and may find an occasional place as a substitute for PAS in cases where serious intolerance to PAS occurs.

Neomycin is considered too toxic for use in the chemotherapy of tuberculosis.

Pulmonary Mycoses

Reports during the past year indicate that both stilbamidine and undecylenic acid have a favorable effect in systemic blastomycosis. The relative infrequency with which the less common mycotic pulmonary conditions are recognized gives no opportunity to observe case series large enough to permit critical analysis. This is a field where the reporting of even one case history is important. As for the more commonly recognized infections, such as coccidioidomycosis, nothing of import has been added. In the treatment of fungal disease of the lung it is considered essential that "antibiotic cocktails," or running the gamut of therapy, be not instituted until a definite diagnosis has been made, since such a procedure not infrequently obscures the correct diagnosis.

Chemotherapy and Antibiotics in Non-Tuberculous Pulmonary Diseases

The following agents are of practical value in the medical management of diseases of the broncho-pulmonary tree: penicillin, streptomycin, the broad-spectrum antibiotics, consisting of aureomycin, terramycin and chloramphenicol, bacitracin, polymyxin, the sulfonamides, and the enzyme solutions, tryptar and varidase.

Penicillin is the drug of choice in the majority of pulmonary infections.

It is most useful against the gram-positive organisms. The best method of administration is the intramuscular route, using 100,000 units every three hours and continuing therapy until temperature is normal for 72 hours. Oral penicillin may be used but in doses five times as large as those used parenterally. It should not be relied upon in severe infections. Neo-Penil, a new penicillin derivative for intramuscular use, produces much larger concentrations of penicillin in lung tissue, and promises to be of considerable value in chronic pulmonary infections due to penicillin-sensitive bacteria.

Streptomycin is of value in pulmonary infections due to gram-negative organisms, particularly Friedlander's bacillus and Pasteurella tularensis. It should be given 1 gram intramuscularly every six hours for the first several days and then 1 gram daily for another week or so. In an occasional patient higher doses may be required.

Aureomycin, terramycin and chloramphenicol, the broad-spectrum antibiotics, all have a very similar action. They are effective in primary atypical pneumonia, ornithosis, rickettsial diseases, bacterial pneumonia, tularemic and Brucella infections, and those due to the salmonella species. Gastrointestinal symptoms and secondary monilial infections are relatively common following the use of aureomycin and terramycin. A dosage of 250 mgm. every six hours instead of the usual 500 mgm. definitely lessens the toxicity of the drugs, without apparently interfering with their effectiveness. Because of the increasing number of reports of aplastic anemia following the use of chloramphenicol, the latter should be used with caution.

Bacitracin is effective in lobar pneumonia, given in doses of 30,000 to 50,000 units every six hours for three to 12 days. Because of its nephrotoxicity, it should be used only in patients whose infections do not respond to penicillin and other less toxic antibiotics.

Polymyxin is effective in infections caused by Ps. Aeruginosa, A. Aerogenes, K. Pneumoniae, Esch. coli and H. Influenzae. It is a toxic drug and should be limited to severe pulmonary infections not responding to other measures.

The sulfonamides have been relegated to a secondary place since the introduction of the antibiotics because of their potential kidney effects. However, they are highly effective in many bacterial infections of the lung and bronchial tubes, due to gram-positive organisms. They may enhance the value of penicillin.

Aerosal antibiotic therapy may be of value in chronic bronchitis, bronchiectasis and lung abscess. Difference in reported results may be due to technique. A recent addition to aerosol therapy is the use of streptococcol enzyme solution and trypsin therapy in the form of a spray. The effectiveness of these enzymes is under investigation.

The enzyme solutions, varidase or tryptar, have now been accepted as valuable adjuncts in the treatment of pyogenic empyema. They are used in conjunction with antibiotic and surgical therapy when the latter becomes necessary.

General Considerations in the Treatment of Bronchopulmonary Infections

Cultures of the sputum should always be obtained when possible. This is particularly important in severe and chronic infections. Sensitivity tests of cultures should be done in serious and long-standing infections that do not respond quickly to therapy.

Indiscriminate use of antibiotics especially in mild infections should be avoided. There are two serious objections to the unnecessary use of such agents. The first is the development of resistant organisms. The second objection is a change in the bacterial flora, such as a predominance of monilial organisms when aureomycin or terramycin is used, or a predominance of gram-negative bacteria following penicillin. Such therapy may upset the balance of nature.

Combined therapy should be used in serious infections when it appears necessary. It should be kept in mind that there is experimental evidence that there may be antagonism between the antibiotics such as penicillin and chloramphenicol. Sensitivity testing may be necessary in severe long-standing infections in order to determine the best possible combinations of therapy.

Karl H. Pfuetze, Chicago, Illinois, Chairman
Benjamin P. Potter, Jersey City, New Jersey, Vice-Chairman
Sumner S. Cohen, Oak Terrace, Minnesota, Secretary
Emil Bogen, Olive View, California
Lloyd B. Dickey, San Francisco, California
Edward Dunner, University City, Missouri
Arthur W. Duryea, St. Louis, Missouri
Alfred Goldman, St. Louis, Missouri
Ralph E. Moyer, Oteen, North Carolina
Charles E. Lyght, Rahway, New Jersey
Edward H. Robitzek, Staten Island, New York
Arnold Shamaskin, Ahwahnee, California
Henry C. Sweany, Tampa, Florida
John V. Thompson, Indianapolis, Indiana.

FIFTIETH ANNIVERSARY OF THE HENRY PHIPPS INSTITUTE

During the week February 2-7, 1953, the Henry Phipps Institute of the University of Pennsylvania celebrated its Fiftieth Anniversary. The Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis was founded in 1903 by the industrialist Mr. Henry Phipps of Pittsburgh, whose interest in tuberculosis was stimulated by Dr. Lawrence F. Flick of Philadelphia, a pioneer in the campaign against tuberculosis in this country. The Institute opened its doors for patients on February 2, 1903. It became a part of the University of Pennsylvania in 1909.

Principal speaker during the afternoon program on February 6, was Dr. J. Burns Amberson, Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York City, who spoke on "The Treatment of Tuberculosis." In the evening Dr. Thomas Parran, Dean of the Graduate School of Public Health, University of Pittsburgh spoke on "The Prevention of Tuberculosis." Dr. Esmond R. Long, Director of the Institute, presided at the evening session.

Addresses Given in Latin America*

ANDREW L. BANYAI, M.D., F.C.C.P.
President American College of Chest Physicians
Milwaukee, Wisconsin

Rio de Janeiro, Brazil, August 23, 1952
Opening Executive Session

It is the greatest thrill of my professional career to address this most illustrious group of chest specialists assembled here today from many lands. I wish to take this opportunity to express to you the thanks and appreciation of the officials and membership of the College for your indefatigable, diligent and energetic work in advancing the interest and further development of the College. Your presence here and your participation in these transactions are a concrete proof that the American College of Chest Physicians is a living, progressive organization with a portant destiny and responsibility in modern medicine. May the College enjoy the benefit of your continued good will and cooperation.

Rio de Janeiro, Brazil, August 24, 1952
Inaugural Address at the Joint Opening Session of the XII Congress of the International Union Against Tuberculosis and of the II International Congress on Diseases of the Chest

It may be truthfully said that the inauguration of the II International Congress on Diseases of the Chest is one of the most momentous events in modern medical history. Scientists have come here from all over the world to present new ideas, new methods, new techniques and new discoveries pertaining to problems of diagnosis and treatment of chest diseases. The transactions and deliberations of this Congress will embrace the presentation of lectures, critical reviews, discussions, demonstrations and motion pictures of pertinent interest, all offered in and permeated by the spirit of creative deeds in the field of medicine and surgery. There have gathered here today leaders of knowledge and teaching in medical sciences, showing their theoretical and practical "wares" as if it were a scientific world's fair. But that is as far as the analogy goes. The information presented here today is not for sale. Its motivation is not profit or monetary reward. On the contrary, all that is done and said here as part of this Congress is but for the advancement of science and for the benefit of mankind.

The II International Congress on Diseases of the Chest is being held in Rio de Janeiro as a homage and tribute of the members of the College to the great scientific accomplishments of the medical profession of Brazil.

*Condensed versions.

In the same manner that heliotropism turns the flowers and leaves of plants toward the sun, we have been attracted to Brazil by the shining light of your magnificent scientific attainments. Just think of Brazilian medical men of prominence, such as Osvaldo Cruz, Carlos Chagas, Gaspar Viena, Ezequiel Diaz, Cardoso Fontes, Recha Lima, Tales Martins, Alvaro and Miguel Osorio, Vital Brasil, Wucherer, Manoel de Abreu and many others. Just think of Brazilian research institutions of world renown, such as the Osvaldo Cruz Institute, with a library of 125,000 volumes, the Butantan Institute of Sao Paulo, the Institute of Tropical Medicine at Belem, the National Institute of Child Health and others. The National Yellow Fever Service of Brazil is world famous. Its control measures have been so successful that they have been adopted all over the world. It is well to mention that the commonly known form of yellow fever, the "urban type," has been completely eradicated in Brazil.

It is with appreciation and admiration I relate that during the Second World War, penicillin produced in Rio de Janeiro and Sao Paulo was shipped to the United States. The Brazilian people in general and the Brazilian medical profession in particular should be justly proud of the present status of medicine in this country.

On this solemn occasion, I want to convey to you, with deep humility and sincerity, our heartfelt thanks and gratitude for your enormous help in making this Congress possible and also, for your splendid and overwhelming hospitality. The II International Congress on Diseases of the Chest is a symbolic expression of the solidarity and unity of medical science of the world. Truly, this Congress is symbolic of the fact that we are all citizens of the free Commonwealth of science. Let us resolve that we will do our utmost to maintain and advance this unity and this citizenship so as to best serve the welfare of mankind.

Rio de Janeiro, Brazil, August 28, 1952
Presentation of the College Medal to Professor Jorgen Lehmann at the II International Congress on Diseases of the Chest

We have been brought together on this auspicious occasion to pay tribute to a great man and a prominent scientist for his epoch-making discovery in the field of chemotherapy for tuberculosis. Because of innumerable trials and failures with various chemical compounds which were used in the management of this disease in the past, chest physicians were living in an atmosphere of rather pessimistic anticipation concerning effective chemotherapy. Then a ray of hope appeared from the Northeast. From the happy union of creative ingenuity and logical reasoning, a great discovery was born.

In 1941, a report appeared in the medical literature, stating that benzoic acid and one of its derivatives, salicylic acid (erthoxybenzoic acid) increased the oxygen uptake of growing tubercle bacilli. This observation prompted attempts at chemical modification of the compound so that it would inter-

fere with the oxygen uptake of this micro-organism. This clue served as the starting point of a purposeful, systematic search for a bacteriostatic agent against the tubercle bacillus. The painstaking investigation which followed climaxed in the needle-sharp observation that when an amino radical was added to the salicylic acid molecule in the para position, the resulting compound was effective in suppressing the growth of tubercle bacilli in culture media. This discovery was made in December 1943. The in vitro studies were followed by experimental work which revealed that the new chemical, para-aminosalicylic acid, was capable of retarding the development of tuberculosis in mice and guinea pigs. Clinical trials with this compound began in March 1944. Since then, numerous publications in the medical literature have confirmed the therapeutic value of para-aminosalicylic acid in pulmonary and extrapulmonary forms of tuberculosis.

We have assembled here tonight to bestow upon the discoverer of this new, effective form of chemotherapy the greatest honor of an international scientific society, the American College of Chest Physicians.

Professor Lehmann, you are the prototype of a true genius. You have seen the light while all of us were groping in the darkness of ignorance. Your uncanny intuition perceived a new means hitherto unfamiliar to medical science. You have created something known from the unknown. You have transformed worthless, white powder into a new, potent medicine which is capable of saving innumerable human lives.

Professor Lehmann, your merit as one of the greatest benefactors of mankind has been indelibly engraved in the annals of medicine.

Professor Lehmann, as a token of our high esteem and sincere admiration for you and for your marvelous achievement, on behalf of the American College of Chest Physicians, I have the distinct honor and privilege to present to you this gold medal and certificate of award.

Presentation of Plaque of Appreciation to Dr. Getulio Vargas, President of Brazil

Your Excellency:

As President of the American College of Chest Physicians and on behalf of the II International Congress on Diseases of the Chest, I consider it an exceptional honor and privilege to address your Excellency.

We are familiar with the fact that the incentive, inspiration and dynamic initiative of your personal attitude have contributed in an extraordinary manner to the phenomenal development of medical science in Brazil.

Your vigorous encouragement of organized institutional research work has resulted in new perspectives, in brilliant success and in a prolific amount of creative work in this field of endeavor.

Your name, Sir, is synonymous with idealism, progress and liberalism in medical education, which are so essential for improving the health of the people.

Under the augury of your regime, Brazilian medicine has reached a prominence upon which physicians throughout the world look with admiration and approbation.

The creation of the Ministry of Education and Health by the Provisional Government under your leadership in 1930 was a concrete expression of your genuine interest in the welfare of this nation.

Your foresight and vision in sponsoring concurrently sanitation and higher education are unparalleled in modern history.

It gives me great pleasure, indeed, to offer you, your Excellency, this plaque of appreciation, which is emblematic of the respect, esteem and admiration of the membership of the American College of Chest Physicians.

Rio de Janeiro, Brazil, August 30, 1952
Address at the Closing Banquet of the II International Congress on Diseases of the Chest

As President of the American College of Chest Physicians it gives me great pleasure to address this splendid and distinguished audience. This magnificent gathering here tonight signifies the termination of two international meetings. To me the glorious sight of your presence at this banquet is as precious as a welcome oasis for the tired wanderer of the desert. It is a gratifying sight, indeed, because, figuratively speaking, for days, while attending the sessions of the Congress, we have been covering vast, unromantic fields of medical science. When we, the anonymous masons who prepared this monumental Congress, take an account of our labors, we can truthfully say we are more than satisfied with the results. We have been well rewarded by the brilliant scientific contributions of famous medical men from this country and from all over the globe. We have been well rewarded by the mutual trust, harmony, understanding and amity which prevailed among the participants of this Congress. We have been well rewarded by the superb beauty of your city, Rio de Janeiro. Its dominantly modern architecture, its picturesque parks and squares with lovely landscaping and pretty lagoons are second to none. Its spacious, scenic drives, its impressive monuments, its colossal public buildings, its theaters and museums are like glimpses from a fairy tale. Your Corcovado and your Pão Açucar are beyond description.

Indeed, from my talks with a great many of the delegates to this Congress, I can categorically say that we have nothing but admiration for the natural attraction, man-made beauty and for the cultural and educational accomplishments of this community. I want to pay special tribute to the health institutions of this city which are outstanding examples of up-to-date scientific orientation and progressiveness. When I think of the great scientific achievements of this Congress, held in this wonderful city, I cannot help recalling the legend of Pygmalion. It is the story of the

sculptor who fell in love with his own masterpiece. I feel this legend applies perfectly to all of us who labored on the creation of this Congress.

We have come to this country as an expression of our appreciation of the marvelous scientific work of the medical profession of Brazil. When time commands us to leave, we shall depart enriched with new knowledge, bound by intangible ties of friendship and imbued with the most precious memory of your splendid hospitality. For all this, we will be ever grateful to you.

Buenos Aires, Argentina, September 5, 1952

This occasion is a unique event in the history of the American College of Chest Physicians and it is going to be so recorded in the annals of medical history, because a large delegation of Fellows of the College has travelled from 6,000 to 9,000 miles to attend this meeting. Although we have come here on our own volition and on our own initiative, we want you to know that we are emissaries of the officials and of the entire membership of the College. We are emissaries of good will, loyalty and solidarity, personally as well as in the field of medical science. We have come to Argentina because we are convinced that we will learn from your knowledge, experience and research work which are so well known to us. We have come here because we expect through formal meetings and through informal exchange of views and opinions to gain—mutually—new ideas, new values, new interests and new perspectives. The participation of such a large group of Fellows from the United States in your scientific endeavors is a concrete expression of the dominant precepts, the governing principles and spirit of this organization. We want you to feel that the American College of Chest Physicians belongs to you as much as you belong to the American College of Chest Physicians. This is the slogan which prompted our coming to you, being with you and working with you.

Santiago, Chile, September 10, 1952

To begin with, I want to express our heartfelt thanks and appreciation for the generous hospitality you are extending to us. I have to confess that your wonderful hospitality is as overwhelming as the magnificent beauty of Nature we have found in your great country.

The records of the annual conventions of the College show that our Chilean colleagues have been consistently interested in attending them in various cities of the United States. At this time, we are very glad to give a concrete demonstration that the College has been anxious to reciprocate. We feel that the size of the delegation of Fellows from the United States is the best expression of the close ties which bind the Chilean Chapter and the parent organization together. This date is going to be a memorable day in the history of medicine, of the American College of Chest Physicians,

and its Chilean Chapter. A red-letter-day, indeed, because it brought us, North Americans, and you, Chilean Gentlemen together in the brotherhood of medical science. Although we have known each other through correspondence, through publications in the medical literature and through occasional personal contacts, reality in the form of our present visit here is bound to strengthen our unity within the College and within the domain of medical science. This meeting has been planned in the spirit of mutual understanding, mutual assistance and perfect collaboration. The presentations to be given here by North American Fellows will bring to you the most recent advances pertaining to various subjects in the specialty of chest diseases. I can assure you that in exchange we intend to learn from you as much as you are graciously willing to offer from your own knowledge and clinical experience.

The officials and the Fellowship of the College want to go on record at this time that it is their ardent hope and desire that international meetings similar to this one will be maintained in the future so as to promote the progress of the College and to enable us to render better service to mankind.

Lima, Peru, September 13, 1952

When plans were made for the II International Congress on Diseases of the Chest, which was concluded at Rio de Janeiro a short while ago, the Executive Board of the College selected your famous capitol city, Lima, as a point of importance where a joint meeting was to be arranged with the Peruvian Chapter of the College. We, the officials and members of the College, are genuinely grateful to our Peruvian colleagues for their excellent cooperation in bringing this plan to fruition. At the same time, I want to express our gratitude and appreciation for the splendid hospitality with which we have been received here.

I am standing on the soil of Peru with deep respect and reverence when I think of this country as one of the oldest, if not the oldest site of human civilization. The exquisite art and natural science of this land in ancient times are known the world over. The marvelous architectural perfection of its early inhabitants is still unsolved and surprising as it is, modern engineering science is still unable to duplicate the construction of permanent stone structures without mortar. With such unprecedented historical background in mind, the present-day outstanding scientific accomplishments of the medical profession of Peru is not a surprise at all; on the contrary, it has been anticipated. Metaphorically speaking, the phoenix has reborn from its ashes: Peruvian medical science is soaring high and triumphant in the realm of human civilization. For this reason, we welcome this unique opportunity of having a large delegation of Fellows of the College from the United States actively to participate in this joint scientific meeting. Let us hope that through this meeting and similar ones in the future we shall build a greater College, we shall enhance the advancement of medical science and we shall aid international peace and cooperation.

Panama City, Republic of Panama, September 16, 1952

When some twenty years ago I first visited your delightful country, with its most famous crossroad of the world, I learned with amazement that here, what most people think is East, is actually West, and vice versa, as far as the Panama Canal is concerned. A similar paradox is represented by the scientific meeting arranged here today. Instead of the members of this Chapter coming to the College, the College has come to you. On the square at your Palace of Justice there is a famous obelisque in memory of the Frenchmen who sacrificed their lives while building the Panama Canal. On this obelisque there is a plaque showing two human figures emerging from the waters of the Atlantic and the Pacific; two human figures joining hands, symbolizing the joining of the two oceans. It reminded me of the fact that our presence in your country is symbolic of the unity of the College and its chapters. It is a remarkable event in the history of the College and for that matter, in the history of any medical group that such a large delegation of its Fellows travel from one country to another. Following the completion of the II International Congress on Diseases of the Chest at Rio de Janeiro, the same group of specialists from the United States participated in scientific meetings in a number of the capitol cities of South America. It may appear that this being the last stop before our returning to the United States, perhaps, it signifies the beginning of the end. I can assure you that the converse is true.

This meeting here in the Republic of Panama signals the beginning of our efforts to intensify the work which has already obtained such excellent results. Similar meetings are now being organized in various parts of the world, the next one to be held in Barcelona, Spain in 1954. Such meetings give promise of creating a better understanding, developing greater scientific progress and superior medical service throughout the world.

REPORT ON THE FIRST INTERAMERICAN CONGRESS OF PUBLIC HEALTH

Havana, Cuba, September 26 - October 1, 1952

As resolved in the XIII Pan American Sanitary Conference, the First International Congress of Public Health convened in Havana September 26 - October 1, 1952.

This Congress marked the fiftieth anniversary of the Pan American Sanitary Bureau and was dedicated to the memory of Dr. Carlos J. Finlay, the Cuban savant whose discovery of the transmission of yellow fever by the mosquito made possible the eradication of this scourge.

The Congress was presided by the Minister of Public Health of Cuba Dr. Enrique Saladrigas. One hundred and forty delegates from all of the North American and several European countries were in attendance.

The official themes were Rural Sanitation, Sanitary Organization and Progress in the Treatment and Control of Communicable Diseases.

Of particular interest to the readers of *Diseases of the Chest* was the symposium of Tuberculosis in which the present status of BCG vaccination in the light of the new chemotherapy of tuberculosis was discussed by Dr. Esmond Long. This paper was commented by Drs. Alfredo Leonardo Brave, Chief of the Department of Tuberculosis, Santiago, Chile and J. Ricardo Martinez, Director, Division of Tuberculosis, El Salvador, members of the American College of Chest Physicians and Dr. Irvin M. Lurie of the Pan American Sanitary Bureau, Washington, D. C.

Antonio Navarrete, M.D., Regent.

Semi-Annual Meeting, Board of Regents

The semi-annual meeting of the Board of Regents of the College was held at the Cosmopolitan Hotel, Denver, Colorado, at 2 p. m. on Monday, December 2, 1952. The following Regents and guests were present:

Donald R. McKay, Buffalo, New York, Chairman, presiding
Robert J. Anderson, Washington, D. C.
Andrew L. Banyai, Milwaukee, Wisconsin
Otto L. Bettag, Chicago, Illinois
Seymour M. Farber, San Francisco, California
Carl H. Gellenthien, Valmora, New Mexico
Alfred Goldman, St. Louis, Missouri
Alfred N. Goldman, Los Angeles, California
Burgess L. Gordon, Philadelphia, Pennsylvania
Alvis E. Greer, Houston, Texas
Edward W. Hayes, Monrovia, California
Willard B. Howes, Detroit, Michigan
William A. Hudson, Detroit, Michigan
Hollis E. Johnson, Nashville, Tennessee
William S. Klein, Denver, Colorado
Aldo A. Luisada, Chicago, Illinois
Louis Mark, Columbus, Ohio
Arnold Minnig, Denver, Colorado
Jay Arthur Myers, Minneapolis, Minnesota
Arthur M. Olsen, Rochester, Minnesota
J. Winthrop Peabody, Washington, D. C.
Charles K. Petter, Waukegan, Illinois
Joseph C. Placak, Cleveland, Ohio
William R. Rumel, Salt Lake City, Utah
James H. Stygall, Indianapolis, Indiana
Charles F. Taylor, Norton, Kansas
Harold G. Trimble, Oakland, California
Harold M. Van Der Schouw, Wheatridge, Colorado
Roy A. Wolford, Washington, D. C.

Murray Kornfeld, Chicago, Illinois, Executive Director
Harriet L. Kruse, Chicago, Illinois, Executive Assistant

Dr. McKay opened the meeting and called for the report of the Treasurer. Dr. Petter read the financial report and budget for 1953 which were duly accepted by the Board.

The report of the Council on Undergraduate Medical Education was presented by Dr. Hayes and was accepted by the Board with an expression of appreciation for the excellent work of the Council.

Dr. Banyai reported on the plans for early publication of the book on nontuberculous diseases of the chest.

The report of the Council on Postgraduate Medical Education was presented by Dr. Peabody. The enrollments of the courses given during the year were reported and announcement was made of postgraduate courses planned for 1953. Dr. Peabody's report was accepted by the Board with thanks.

Dr. Greer presented the report of the Board of Examiners and made a number of recommendations for the improvement of the conduct of Fellow-

ship examinations. Dr. Mark moved that a committee be set up to study Dr. Greer's recommendations. The report of Dr. Greer and the motion by Dr. Mark were accepted by the Board.

Dr. Trimble reported for the Council on Research and announced that two meetings had been held since the annual meeting of the College last June with all or a majority of the members present at each meeting. He reported briefly on the activities of the Committee on Non-surgical Collapse Therapy, of which he serves as chairman. Dr. Luisada, a member of the Committee on Cardiovascular Disease, was then requested to present his proposal for the establishment of a research fellowship in cardiopulmonary physio-pathology, which had been approved by the Council on Research at its last meeting. It was moved that the recommendation be referred to the Executive Council for proper action. Dr. Goldman suggested that if the fellowship is established, the laboratory of Dr. Myron Prinzmetal be used for the second year of training. Dr. Goldman reported on the activities of his Committee on Surgical Treatment of Diseases of the Chest and Dr. Olsen presented his report of the Committee on Bronchoesophagology. Dr. Trimble read the report prepared by Dr. Karl H. Pfuetze, Chairman of the Committee on Chemotherapy and Antibiotics, who was not able to be present. The report of the Council on Research, as well as the reports of the committees serving under the Council, were accepted by the Board.

Dr. McKay introduced Dr. Arnold Minnig of Denver who was chairman of the Interim Session meeting sponsored by the Rocky Mountain Chapter of the College, and the Board extended a vote of thanks to Dr. Minnig for the excellent meeting he had arranged. Dr. William S. Klein, Medical Director of the J.C.R.S. Sanatorium at Spivak, Colorado, was introduced and extended the appreciation of the Board for the dinner and x-ray conference he had arranged at the sanatorium for Sunday evening, November 30. An expression of appreciation from the Board was also extended to Dr. Sidney H. Dressler, Medical Director of the National Jewish Hospital, who was not present, for the tour of the hospital which had been arranged for the Board of Regents and the luncheon given for them at the hospital that morning. Dr. Harold M. Van Der Schouw, Medical Director of the Lutheran Sanatorium at Wheatridge, was introduced. Dr. Van Der Schouw expressed regret that the lack of time did not permit a visit by the Board members to his hospital. Dr. Carl W. Tempel, President of the Rocky Mountain Chapter of the College, was given a vote of thanks for his fine cooperation in handling the scientific assembly.

Dr. Myers presented the report of the Committee on Membership and the report of the Editorial Board for *Diseases of the Chest*. Both reports were accepted by the Board of Regents with appreciation.

In the absence of Dr. R. S. Anderson, Chairman of the Council on Hospitals, Dr. Bettag presented the report of that Council. A resolution was read proposing that a news release be prepared for medical directors of tuberculosis hospitals and sanatoria. Dr. Bettag presented a report of the Committee on Chest Diseases in Institutions and announced the dedication of the H. A. Burns Memorial Unit, the tuberculosis section of the Anoka

Hospital for Mental Diseases in Minnesota, which he attended with members of the College in Minnesota. The reports presented by Dr. Bettag were accepted by the Board.

Dr. Bettag then presented the report of the Joint Committee on Chest X-ray which consisted of two additions to the report of the committee as published in the June, 1952 issue of *Diseases of the Chest*. The report was approved by the Board of Regents of the American College of Chest Physicians and referred to the American College of Radiology for approval by their Board of Chancellors. The complete report will be published in an early issue of the College journal.

Dr. Robert J. Anderson was called upon to present his report of the Council on Public Health. This report was accepted by the Board. Dr. Anderson then announced that the Committee on BCG had held a meeting in Rio de Janeiro, during the II International Congress on Diseases of the Chest, and stated that the report of the committee should be available for presentation at the next annual meeting of the College.

Dr. Greer, Chairman of the Finance Committee of the Council on Research, presented a report of his committee and plans for future activities. The report was unanimously accepted by the Board of Regents.

In the absence of the chairman, Dr. Mark read the report of the Joint Committee on Industrial Diseases of the Chest, which was duly accepted by the Board.

Dr. Rumel, Chairman of the Board of Governors of the College, was called upon and made some brief remarks concerning the activities of the Board.

The Chairman of the Committee on Scientific Program for the next annual meeting of the College, Dr. Arthur M. Olsen, outlined with the use of a blackboard the plans for the scientific program. The Board of Regents congratulated Dr. Olsen upon the excellent program being arranged.

Dr. Trimble, Chairman of the Committee on College Award, presented the name of the proposed recipient of the next College Medal. The Board unanimously approved the choice of the Committee.

A resolution was presented recommending that Honorary Fellowship in the College be awarded to the Surgeon Generals of the U. S. Army, U. S. Navy, U. S. Air Force and the U. S. Public Health Service, as well as to the Chief Medical Director of the Veterans Administration. The resolution was duly accepted by the Board.

Mr. Kornfeld read a letter received from Dr. Arden Freer, Acting Medical Director of the Veterans Administration, announcing his retirement and recommending Dr. Roy A. Wolford, his successor in office, for appointment as Governor of the College for the Veterans Administration. The resignation of Dr. Freer as Governor of the College for the Veterans Administration was accepted by the Board with regret. Dr. Banyai, President of the College, thereupon appointed Dr. Wolford as the Governor of the College for the Veterans Administration.

Announcement was made that the 19th Annual Meeting of the College would be held at the Hotel New Yorker, New York City, May 28 through 31, 1953. The meeting was then adjourned.

19th Annual Meeting
American College of Chest Physicians

HOTEL NEW YORKER, NEW YORK CITY
MAY 28 - 31, 1953

PRELIMINARY SCIENTIFIC PROGRAM

General Session, Thursday Evening, May 28:

"Recent Developments Concerning Penicillin and Allied Antibiotics,"
Sir Alexander Fleming, London, England.

"Problems in Diseases of the Esophagus,"
Chevalier L. Jackson, Philadelphia, Pennsylvania.

"The Diagnosis and Management of Chylothorax,"
Roy G. Klepser and James F. Berry, Washington, D. C.

"The Management of Spontaneous Pneumothorax,"
L. M. Shefts and Capt. C. Gilpatrick, Fort Sam Houston, Texas.

(Additional papers to be announced).

Friday Morning, May 29:

Symposium on Pulmonary Function and Physiologic Therapy

"Degenerative Lung Disease,"
Gerald L. Crenshaw, Oakland, California.

"Pulmonary Function in Different Postures—Therapeutic Considerations,"
Zoltan Mann, Fort Bayard, New Mexico.

"The Clinical Use of Intermittent Positive Pressure Breathing Combined with Nebulization in Chronic Pulmonary Disease,"
Peter A. Theodos, Philadelphia, Pennsylvania.

"The Use of Proteolytic Enzyme Aerosols,"
L. Chandler Roettig, Columbus, Ohio.

"The Visco-Elastic Properties of the Lungs in Emphysema,"
J. Mead and J. L. Whittenberger, Boston, Massachusetts.

Panel Discussion:

Edwin R. Levine, Chicago, Illinois, Moderator
Alvan L. Barach, New York, New York
Hurley L. Motley, Los Angeles, California
George G. Ornstein, New York, New York
Maurice S. Segal, Boston, Massachusetts
J. L. Whittenberger, Boston, Massachusetts
George W. Wright, Saranac Lake, New York

Friday Afternoon, May 29:

Symposium on Electrocardiography—Panel Discussion

"The Normal Electrocardiogram,"
Louis Wolff, Boston, Massachusetts.

"The Electrocardiogram of the Normal Child and of the Child with Congenital Heart Disease,"
Jakub G. Schlichter, Chicago, Illinois.

"The Electrocardiogram in the Disturbances of Cardiac Rate and Rhythm,"
Richard Langendorff, Chicago, Illinois.

"Diagnostic Electrocardiographic Patterns,"
Arthur M. Master, New York, New York.

"Non-Diagnostic Electrocardiographic Patterns,"
Nathaniel Reich, Brooklyn, New York.

"The Clinical Value of Electrocardiography,"
Aldo A. Luisada, Chicago, Illinois.

Symposium on the Rehabilitation of the Cardiac Patient

Subjects: "The Traumatic Cardiopathies,"
"The Medical Rehabilitation of the Cardiac Patient for Work,"
"The Surgical Rehabilitation of the Cardiac Patient for Work,"
"Methods of Evaluating Work Capacity of Cardiac Patients,"

Panel Discussion:

John F. Briggs, St. Paul, Minnesota, Moderator
Charles P. Bailey, Philadelphia, Pennsylvania
Claude Beck, Cleveland, Ohio
John G. Bielawski, Detroit, Michigan
Arthur M. Fishberg, New York, New York
Jere W. Lord, New York, New York
Arthur M. Master, New York, New York
H. Easton McMahon, New York, New York
E. Sterling Nichol, Miami, Florida

Friday Evening, May 29:

Motion Picture Session on Diseases of the Chest,
Paul H. Holinger, Chicago, Illinois, Chairman.

Physicians having interesting films for presentation in this session are invited to communicate with Dr. Paul H. Holinger, 700 North Michigan Avenue, Chicago 11, Illinois.

Saturday Morning, May 30:

Symposium on Occupational Diseases of the Chest—Panel Discussion

Moderator: Raymond B. Hussey, Chicago, Illinois.

"Soft Coal Workers' Pneumoconiosis,"
Louis L. Friedman, Birmingham, Alabama.

"Physiologic Therapy,"
Burgess L. Gordon, Philadelphia, Pennsylvania.

"Environmental Dust Control,"
Leonard Greenburg, New York, New York.

"Berylliosis,"
Harriet L. Hardy, Boston, Massachusetts.

"Rehabilitation,"
Louis Mark, Columbus, Ohio.

"Pulmonary Function,"
George R. Meneely, Nashville, Tennessee.

"Medicolegal Aspects,"
William E. Mitch, Birmingham, Alabama.

"Roentgenographic Characteristics,"
Oscar A. Sander, Milwaukee, Wisconsin.

"Diatomaceous Earth,"
Reginald H. Smart, Los Angeles, California.

"Etiology, Pathology and Pathogenesis,"
Arthur J. Vorwald, Saranac Lake, New York.

"Medicolegal Aspects,"
Theodore C. Waters, Baltimore, Maryland.

Saturday Afternoon, May 30:

"The Papworth Village Settlement,"
Richard R. Trail, London, England.

"Surgery of Pulmonary Stenosis by the Direct Intra-Cardiac Approach,"
Robert P. Glover, Philadelphia, Pennsylvania.

X-Ray Conference

Laurence Robbins, Boston, Massachusetts, Moderator.

Sunday Morning, May 31:

Tuberculosis

"Pulmonary Resection in Childhood Tuberculosis,"
Gladys Boyd, Toronto, Canada.

"Isoniazid in Tuberculous Meningitis,"
Mark Lepper, Chicago, Illinois.

"Isoniazid in the Treatment of Pulmonary Tuberculosis,"
Ralph E. Moyer, Oteen, North Carolina.

"Right Heart Failure in Chronic Pulmonary Disease,"
Speaker to be announced.

Panel Discussion:

"When is Resection Indicated in Patients who have had Prolonged Chemotherapy for Pulmonary Tuberculosis?"
Moderator to be announced
Robert G. Bloch, New York, New York
David A. Cooper, Philadelphia, Pennsylvania
Edgar Medlar, Ithaca, New York
Richard H. Overholt, Brookline, Massachusetts
William Steenken, Trudeau, New York.

Sunday Afternoon, May 31:

Symposium on Postoperative Management in Thoracic Surgery

"Postoperative Management of Bronchopleural Fistula and the Pleural Space Following Pneumonectomy,"
Otto C. Brantigan, Baltimore, Maryland.

"Postoperative Management of Cardia Arrest,"
Julian Johnson, Philadelphia, Pennsylvania.

"Postoperative Management of the Unexpanded Lung Following Pulmonary Resection,"
John B. Grow, Denver, Colorado.

"Postoperative Management of Disturbed Pulmonary Function by Overdistention of the Lung,"
O. T. Clagett, Rochester, Minnesota.

"Pulmonary Edema, Etiology and Therapy,"
E. J. Beattie, Chicago, Illinois.

"Interference with Nervous, Vascular and Pulmonary Structures During Surgery of the Lung,"
Alfred N. Goldman, Beverly Hills, California.

Panel Discussion:

John H. Gibbon, Jr., Philadelphia, Pennsylvania, Moderator
E. J. Beattie, Chicago, Illinois
Otto C. Brantigan, Baltimore, Maryland
O. T. Clagett, Rochester, Minnesota
Alfred N. Goldman, Beverly Hills, California
John B. Grow, Denver, Colorado
Julian Johnson, Philadelphia, Pennsylvania

ROUND TABLE LUNCHEON DISCUSSIONS

The following subjects have been tentatively selected for discussion at the round table luncheons to be held on Friday, Saturday and Sunday, May 29, 30 and 31. Panel members and moderators will be announced at a later date.

"The Substitute Heart and/or Lung"
"Esophageal Obstruction"
"Ill Effects of Overdistension Following Pulmonary Resection and Means of Preventing Overdistension"
"Non-Bronchogenic Cystic Lung Disease; Surgical Management"
"Present Status of Cardiac Surgery"
"Rehabilitation of the Patient with Chest Disease"
"Advances in the Treatment of Hypertension"
"Advances in the Treatment of Cardiac Arrhythmias"
"Mechanical Aids to Respiration
"Present Status of ACTH and Cortisone in Diseases of the Chest"
"Physiologic Management of Bronchial Asthma and Pulmonary Emphysema"
"Management of Bronchiectasis"
"Influence of Location of Disease on the Treatment of Pulmonary Tuberculosis"
"Current Treatment of Pneumonia"
"Home Treatment vs. Sanatorium Care in Tuberculosis"
"Treatment of Pulmonary Tuberculosis in the Very Young and Very Old"
"Present Status of Isoniazid in Tuberculosis"
"Medicolegal Aspects of Pneumoconiosis"

COMMITTEE ON SCIENTIFIC PROGRAM

Arthur M. Olsen, Rochester, Minnesota, Chairman
William E. Adams, Chicago, Illinois
John F. Briggs, St. Paul, Minnesota
Leonard C. Evander, Lockport, New York
Louis L. Friedman, Birmingham, Alabama
Roger S. Mitchell, Saranac Lake, New York
Karl H. Pfuetze, Chicago, Illinois
Maurice S. Segal, Boston, Massachusetts.

ENTERTAINMENT OF LADIES PLANNED FOR ANNUAL MEETING

Doctors, please bring the following information to the attention of your wives. Mrs. Edgar Mayer, Chairman of the Ladies Reception Committee for the 19th Annual Meeting of the College, has announced that the following program has been tentatively planned:

Thursday, May 28:

Morning: Tour of the United Nations.
Afternoon: Theater — "Cinerama".
Tickets for "Cinerama" must be obtained by advance reservation.

Friday, May 29:

Luncheon and Fashion Show, Cotillion Room, Hotel Pierre.

Saturday, May 30:

Morning: Boat trip around New York Harbor.
Evening: Convocation.
Cocktail Party.
Presidents' Banquet.
Saturday evening functions will be held at the Hotel New Yorker, meeting headquarters.

Ladies Reception Committee

Mrs. Edgar Mayer, Chairman
Mrs. Foster Murray, Vice-Chairman

Mrs. Alvan L. Barach
Mrs. Arthur J. Cracovaner
Mrs. J. Maxwell Chamberlain
Mrs. James S. Edlin
Mrs. Irving J. Kane
Mrs. Anthony J. Lanza
Mrs. Charles E. Hamilton
Mrs. George G. Ornstein
Mrs. Coleman B. Rabin
Mrs. Nathaniel E. Reich
Mrs. Charles W. Rieber
Mrs. Eward Robitzek
Mrs. Samuel A. Thompson
Mrs. Arthur S. W. Touroff
Mrs. Harry Vesell

College Chapter News

NORTH CAROLINA CHAPTER

The North Carolina Chapter held a successful 3rd annual meeting October 23, 1952 at which the following officers were elected to serve during 1953:

Leon H. Feldman, Asheville, President
Ralph E. Moyer, Oteen, Vice-President
Norman L. Anderson, Asheville, Secretary-Treasurer.

PACIFIC NORTHWEST CHAPTER

A combined meeting of the Pacific Northwest Chapter and the Trudeau Society was held Nov. 14-15, 1952 at which the following chapter officers were elected:

Cedric Northrop, Seattle, Washington, President
John E. Tuhy, Portland, Oregon, Vice-President
John E. Nelson, Seattle, Washington, Secretary.

CUBAN CHAPTER

The Cuban Chapter of the College held a scientific meeting at the Curie Hospital, Havana, Friday, November 7, 1952. Dr. J. J. Llambes Estrada, Director of the Hospital, presided and the following program was presented:

Case histories on clinical-pathological problems.

Three members were chosen to diagnose the cases.

Cases were illustrated with anatomic and histopathologic samples

Discussion followed each case presentation.

Panel: J. Bolivar Ferrer, M. Betancourt Rodriguez, R. Moreno Montes de Oca, R. Fuste Amieba, F. Leon Blanco, E. Marrero Lopez, R. Sotorrio and R. D. Rumbaut.

ILLINOIS CHAPTER

The Illinois Chapter of the College held a joint meeting with the Chicago Roentgen Society at the University Club, Chicago, Illinois on Thursday, January 8, 1953. The speaker of the evening was Dr. Richard H. Overholt, Brookline, Massachusetts, Past President of the American College of Chest Physicians.

Dr. Benjamin D. Brown, President of the Roentgen Society, presided at the meeting and introduced Dr. John H. Gilmore of the Illinois Masonic Hospital and Dr. William King of Hines Hospital who presented case reports.

Two hundred and fifty physicians attended the meeting. The next meeting of the Illinois Chapter will be given by the University of Chicago Clinics in February.

INDIANA CHAPTER

The Indiana Chapter held a luncheon meeting October 29, 1952. Dr. Thomas R. Owens of Muncie, President of the chapter presided. About 50 members and guests were present to hear a symposium on "The Tuberculosis Problem in the Mental Hospital" by the following doctors: John Larson, Logansport; Foss Schenk, Logansport; John V. Thompson, Indianapolis; and Edwin R. Eaton, Indianapolis.

The following officers were elected for 1953:

John N. Ewbank, Richmond, President
Edward W. Custer, South Bend, President Elect
H. B. Pirkle, Rockville, Secretary.

NEW JERSEY CHAPTER

The New Jersey Chapter will hold a meeting February 24, at 8:30 p.m., at the Roosevelt Hospital for Chest Diseases, Metuchen, New Jersey. Dr. Charles P. Bailey, Professor and Head of the department of Thoracic Surgery at Hahnemann Medical College and Hospital, Philadelphia, will speak on "Recent Advances in Cardiac Surgery."

An executive meeting of the New Jersey Chapter was held November 18, 1952 at the Bonnie Burn Sanatorium.

The annual meeting of the Chapter will take place at Haddon Hall, Atlantic City, New Jersey on May 20, 1953, in conjunction with the meeting of the State Medical Society.

NEW ENGLAND STATES CHAPTER

The New England States Chapter of the College has been holding joint meetings with the Overholt Clinic at the Deaconess Hospital, Boston, every month. On December 14 Dr. Lamar Souther was the guest speaker and his subject was "Results of Lobectomy and Pneumonectomy in Carcinoma of the Lung." Dr. Wilford Neptune was the speaker on January 21 and talked on the subject of "Hypothemia and Repair of Interatrial Septal Defects." The next joint meeting will be held on February 18 and Dr. Morris Rubin will present the subject of "Resection for Pulmonary Tuberculosis in Children."

PERUVIAN CHAPTER

The Peruvian Chapter of the American College of Chest Physicians, at a meeting held in Lima in November 1952, elected the following officers for the 1953 term:

Leopoldo Molinari B., President
Ramon Vargas Machuca, Vice-President
Alejandro Flores Degregori, Secretary
Luis E. Hubner, Treasurer.

URUGUAY CHAPTER

The Uruguay Chapter of the College, under the Presidency of Professor Nicholas L. Caubarrere, held a meeting on November 28, 1952 in Montevideo. The following scientific program was presented:

"Serous Cyst of the Lungs,"
Juan Soto Blanco.
"Variances in X-Ray Films of Cavities Treated with Isodiacin Administered Orally,"
Raul Pintos Fuentes.
"Pulmonary Manifestations of Paracoccidiodomicosis,"
Jose Cancela Freijo.
"Caseous Sinovitis of the Flexor Tendons in a Fistulous Hand Treated with Paraminosalicylic Acid,"
Ramon Marin Pittaluga.
"Osteoblastic Pulmonary Metastasis of an Osteogenic Sarcoma,"
Felix Leborgne.
"Segmentary Resections in the Treatment of Tuberculosis,"
Alejandro Victorica.
"Presentation of a Case of Bronchial Adenoma,"
Nicolas L. Caubarrere and Juan Carlos Dighiero.

College News Notes

Dr. Hugh E. Claremont of London, England has been awarded the S. H. Camp & Company Fellowship for one year's postgraduate training in diseases of the chest at the Manhattan General Hospital, New York City.

Dr. George Schwartz of New York City was recipient of the Bronx *Outstanding Citizen Award* for 1952, given annually by the Bronx Lion's Club, for outstanding civic, welfare and patriotic work. Dr. Schwartz is a member of the Committee on Membership of Greater New York City of the American College of Chest Physicians.

Dr. Harry Shubin, Chief Consultant at the Philadelphia Hospital for Contagious Diseases, recently addressed the staff of the San Angel Sanatorium in Mexico City on the subject "Recent Advances in Therapy of Pulmonary Tuberculosis."

Dr. Arthur M. Olsen of Rochester, Minnesota, presented a paper entitled, "A Discussion of the Common Pulmonary Diseases," before the Postgraduate Assembly of the Sixth Councilor District of the Ohio State Medical Association on October 29, 1952.

The Society of Medical Jurisprudence held a meeting at the New York Academy of Medicine Building on December 8. A motion picture on "A Trip Through the Bronchial Tract" was presented by Dr. Arthur Q. Penta of Schenectady, followed by a discussion from the Medical, Legal and Surgical Standpoints.

Professor Basil N. Papanicolaou, Fellow of the American College of Chest Physicians and Medical Director of the Chest Institute of Athens, Greece, has been appointed a member of the Expert Advisory Panel on Tuberculosis of the World Health Organization.

COLLEGE EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

19th Annual Meeting, American College of Chest Physicians, Hotel New Yorker, New York City, May 28-31, 1953.

POSTGRADUATE COURSES

Postgraduate Course, Diseases of the Chest for General Practitioners, Milwaukee, Wisconsin, March 4, 11, 18, 25, 1953.

6th Annual Postgraduate Course on Diseases of the Chest, Philadelphia, Pennsylvania, March 23-27, 1953.

8th Annual Postgraduate Course on Diseases of the Chest, Chicago, Illinois, September, 1953.

6th Annual Postgraduate Course on Diseases of the Chest, Hotel New Yorker, New York City, November 2-6, 1953.

CHAPTER MEETINGS

Potomac Chapter Meeting, White Sulphur Springs, West Virginia, April 10, 1953.

Florida Chapter Meeting, Hollywood, Florida, April 26, 1953.

13th Annual Meeting, New York State Chapter, Hotel Statler, Buffalo, New York, May 7, 1953.

MEDICAL SERVICE BUREAU

POSITION WANTED

Male Tuberculosis Specialist seeks position with institution. Experienced in collapse therapy, thoracoscopy, bronchoscopy, radiology, and BCG. Canadian citizen. Please address all inquires to Box 268B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Male physician, 52, Canadian graduate, passed Alabama State Boards, seeks residency in tuberculosis hospital or sanatorium. Served as resident in Canadian tuberculosis hospital for 3 years. Please address inquiries to Box 269B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Male physician, F.C.C.P., Georgetown University graduate, age 36, married, 4 children, now in service with the U. S. Army, will be released in August 1953, desires position in California. Experienced in TB. Please address Box 270B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11 Illinois.

POSITIONS AVAILABLE

Resident Physician wanted. Tuberculosis experience essential. Call or write Deborah Sanatorium, Browns Mills, New Jersey.

Resident Physician—for active Thoracic Surgery service. Salary commensurate with experience, includes maintenance. Tuberculosis Hospital. Apply State Tuberculosis Hospital Commission, New State Office Building, Frankfort, Kentucky.

Assistant Medical Director wanted for 200 bed Tuberculosis Hospital, approved by American College of Surgeons. Applicant must have experience in tuberculosis field and be eligible for Michigan license. Excellent salary and generous fringe benefits offered. Please address Box 261A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

DR. POTTENGER HONORED

Dr. Francis M. Pottenger of Monrovia, California, founder of the Southern California Anti-Tuberculosis League, was recently honored at a testimonial dinner in Los Angeles, marking his 50th year of service to the league. He was presented with the first copy of his autobiography, "The Fight Against Tuberculosis," just published. Dr. Pottenger joined the faculty of the University of Southern California in 1903 and became professor emeritus of medicine in 1942.

PERUVIAN TUBERCULOSIS SOCIETY

The following were elected officers of the Peruvian Tuberculosis Society (Sociedad Peruana de Tisiologia) for the year 1952-1953:

Mario Pastor Balcazar, President
Pedro Baldeon P., Vice-President
Juan J. Arredondo and Remigio Aguirre Dongo, Secretaries
Carlos Lopez Ore, Treasurer
Alejandro Vargas Calderon, Librarian.

REPORT OF THE SECOND SESSION OF THE REGIONAL COMMITTEE FOR EUROPE - WORLD HEALTH ORGANIZATION, LISBON, PORTUGAL, SEPT., 1952

The Tuberculosis Program for 1954 included the following points:

Austria: Continuation of the 1953 program. The use of an expert adviser for three months and the allocation of two scholarships for six to 12 months.
Finland: Technical assistance, as in 1953. Funds for an expert adviser for two months for three six-month scholarships and supplies.
Greece: To continue, for six months, the 1953 program. Medical and nursing staff, two six-month scholarships and teaching material.
Trieste: Three scholarships, two for six months and one for one month.
Jugoslavia: An expert-adviser for two months and 17 scholarships from three to six months.

Prof. Lopo de Carvalho
Dr. Lopo de Carvalho Cancella de Abreu

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Ritter J. S. and Bloomberg, H.: J. Urology 1932, 67, 543-546.

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